REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
2009	Open Literature – Book Chapter	

4. TITLE AND SUBTITLE
Medical management of chemical toxicity in pediatrics

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Hilmas, E, Hilmas, CJ

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

US Army Medical Research Institute of Chemical Defense
ATTN: MCMR-CDT-N
3100 Ricketts Point Road
Aberdeen Proving Ground, MD
21010-5400

8. PERFORMING ORGANIZATION REPORT NUMBER

USAMRICD-P09-003

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

US Army Medical Research Institute of Chemical Defense
ATTN: MCMR-CDZ-I
3100 Ricketts Point Road
Aberdeen Proving Ground, MD
21010-5400

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES
Published in Handbook of Toxicology of Chemical Warfare Agents (ed. R.C. Gupta), 919-950, Academic Press: London, 2009.

14. ABSTRACT
See reprint.

15. SUBJECT TERMS
Medical management, chemical warfare agents, exposure, treatment, pediatrics

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Corey Hilmas
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UNLIMITED	32	**19b. TELEPHONE NUMBER** *(include area code)* 410-436-2563

CHAPTER 61

Medical Management of Chemical Toxicity in Pediatrics

ELORA HILMAS AND COREY J. HILMAS

Opinions, interpretations, conclusions, and recommendations are those of the author(s) and are not necessarily endorsed by the US Army.

I. INTRODUCTION

There are essentially millions of chemical compounds known to humanity, but only a limited number are weaponized by conventional militaries. The Organization for the Prohibition of Chemical Weapons (OPCW), the 184-member watchdog agency enforcing the guidelines of the Chemical Weapons Convention (CWC), has identified 55 chemical agents and their precursors that can be used as weapons (OPCW, 2005). Although some of the chemicals are well known (e.g. sarin, soman, VX, mustard), other less obvious choices for chemical terrorism include industrial chemicals such as chlorine and toxic precursors, which are considered "weapons of opportunity".

In the hands of terrorists, chemical warfare agents (CWAs) and toxic industrial chemicals (TICs) pose significant threats to civilian populations. A 2002 report to Congress by the Central Intelligence Agency reported that terrorist groups "have expressed interest in many toxic industrial chemicals – most of which are relatively easy to acquire and handle – and traditional chemical agents, including chlorine and phosgene" (DCI, 2002). While traditional CWAs like nerve agents are attractive to terrorist groups, these agents require a significant degree of financial resources and capital knowledge to manufacture. Furthermore, the USA and remaining signatory members of the CWC have pledged nonproliferation of CWAs (OPCW, 2005). Unfortunately, millions of tons of TICs continue to be manufactured annually in the USA alone. While they support the wide variety of products generated on a daily basis, including dyes, textiles, medicines, solvents, plastics, paints, and insecticides, they are lethal compounds in the hands of terrorists.

Chemical terrorism is the intentional use of toxic chemicals to inflict mass casualties on an unsuspecting military or civilian population, including children. Such an incident could quickly overwhelm local and regional public health resources and emergency medical services. In addition to utilization of CWAs and TICs, an act of chemical terrorism may involve targeting of industrial factories, tanker cars, or vehicles containing toxic substances with conventional explosives near residential communities or schools. Regardless of the methods used, the release of toxic chemicals by terrorists embodies a real and serious threat to our national security and public health. They can quickly incapacitate those who are exposed and can lead to mortality if not recognized and treated promptly. Moreover, the toxicity of these agents can be enhanced in children due to pediatric vulnerabilities. It is imperative to recognize the different ways children may present with toxicity compared to adults.

II. BACKGROUND

Even though many efforts have been made to protect our nation from threats of terror, it is still paramount for our scientific community to continue building our knowledge base regarding CWAs and better understand the toxicities that can occur when children are exposed. Unfortunately, pediatric treatment recommendations are often extrapolated from adult data, even though it is well recognized that pediatric patients should not be regarded as miniature adults. Children present unique vulnerabilities to these chemicals, and special considerations should be taken.

Due to the possibility of pediatric casualties from chemical agent attacks, several pediatric advocacy groups, such as the American Academy of Pediatrics (AAP), have commented on the urgent need for pediatric chemical casualty research (Blaschke and Lynch, 2003). The Committees on Environmental Health and Infectious Diseases have provided the following consensus statement regarding children and chemical–biological threats (CEH/CID, 2000).

> Because children would be disproportionately affected by a chemical or biological weapons release, pediatricians must assist in planning for a domestic chemical–biological

incident. Government agencies should seek input from pediatricians and pediatric subspecialists to ensure that the situations created by multiple pediatric casualties after a chemical–biological incident are considered.

After September 11, the AAP initiated a number of initiatives to try to address the need to prepare for terrorism against children. For example, the AAP created a Task Force on Terrorism, a comprehensive web resource to disseminate information on terrorism and its impact on children. In addition, the AAP has published several reports and policy statements to provide guidance for health care practitioners preparing for a mass chemical casualty event. These efforts were augmented by the passage of several key Federal legislative acts aimed at improving public health emergencies and their response to chemical terrorism. Finally, the Centers for Disease Control and Prevention created the Strategic National Stockpile site (SNS) as a national repository of antibiotics, chemical antidotes, and antitoxins. The SNS contains a pediatric formulary along with compounding materials that would assist clinicians in creating dosage forms appropriate for pediatric administration of chemical antidotes (CEH/CID, 2006) in the event of chemical terrorism.

Indeed, chemical terrorism on US soil is a very sobering possibility in the future. A significant subset of casualties from a mass chemical exposure event will comprise vulnerable populations such as children and the elderly. In the hopes of better understanding the impact of such an event, it is necessary to learn from historical incidents and case studies where children were exposed to toxic chemicals and treated.

In this chapter, the CWAs and "weapons of opportunity" most likely to be used by terrorists to inflict casualties will be examined, following a brief historical account and unique challenges of managing pediatric chemical casualties. The sections for each chemical agent will highlight the pediatric-relevant vulnerabilities and guidelines for medical management. The final two sections will discuss decontamination of children and recommendations to help prepare health care managers and providers in the event of a chemical event. It is hoped that this compilation will provide the necessary guidance and treatment recommendations on how best to treat children involved in a chemical attack.

III. HISTORY OF PEDIATRIC CHEMICAL CASUALTIES

Historically, chemical attacks were limited to the battlefield, and casualties were predominantly military personnel. In turn, the majority of our knowledge concerning management of chemical casualties has come from the experiences of treating our military population. Today, the threat of chemical use is extended to civilian populations as state and nonstate sponsored terrorists target innocent civilians. The risk of chemical and biological terrorism is more tangible since the events of September 11, 2001 and the intentional spread of anthrax through the US Postal Service. Terrorists expanded their scope and threat to inflict mass civilian casualties on a scale never before seen. The threat from attack has moved away from the traditional battlefield to the home front. Innocent civilians, including children, are now prime targets for groups to foment terror and destabilize governments. Even before the attack on the World Trade Center towers, the 20th century witnessed numerous instances where civilian populations were exposed to toxic chemicals or targeted on a grand scale.

During the flurry of chemical barrages across trench lines in World War I (WWI), children from bombed towns in France and Belgium were treated at British, French, and American "gas" hospitals as a result of CWA exposure. Numerous reports of civilian casualties from mustard, chlorine, and phosgene are well documented in British archives (Thomas, 1985). After the final tally of civilian casualties from "gas warfare" was complete, participants saw how ill-prepared their civilians were against such weapons. School-age children learned the importance of protective measures against chemicals through donning of gas masks and evacuating contaminated areas (Figure 61.1).

Civilians have been unintended and, in some cases, intended targets of CWAs since World War I. While cyanide

FIGURE 61.1. School-age girl with US civilian noncombatant gas mask MI-I-I, child size. Photograph: courtesy of the US Army Research Development and Engineering Command, Historical Research and Response Team, Aberdeen Proving Ground, MD.

was used on Jewish prisoners in World War II, chemical weapons would not be used again during combat on civilian populations until the Iran–Iraq War. In the spring of 1987, Saddam Hussein bombed the Iranian city of Sardasht with mustard munitions, resulting in thousands of civilian casualties (Foroutan, 1996a, b, 1998a, b, c).

Following the attack on Sardasht, Iraq attacked Kurd settlements in early 1988, leading to the infamous attack on Kurdish residents of Halabja in March. Thousands of innocent civilian ethnic Kurds perished during the chemical attack, including 75% women and children. Mustard and nerve agents were dropped on civilians from helicopters and planes, and eyewitnesses reported large smoke clouds causing great morbidity and mortality among children (Hay and Roberts, 1990).

Most recently, there have been incidents in the USA where food has been intentionally contaminated with chemical insecticides. Not surprisingly, children were affected in these incidents. One incident occurred in 1998, where a restaurant's salt supply was contaminated with methomyl, a carbamate insecticide. It was reported that five children became ill after eating the insecticide-contaminated food (Buchholz *et al.*, 2002). In another incident that occurred in 2003, approximately 200 pounds of ground beef were contaminated at a grocery store in Michigan with an insecticide called Black Leaf 40. Approximately 90 people (age range 1–76 years) became ill after ingesting the contaminated beef.

These events confirm the devastating reality that chemical threats pose to our unprotected population today. A military and civilian response to the use of chemical weapons on American soil may not be a matter of if but rather a question of when. These events underscore the need for all pediatric-related health care workers to prepare for a mass casualty incident involving CWAs or TICs.

IV. CHALLENGES TO MANAGING PEDIATRIC CHEMICAL CASUALTIES

A. Overview

Managing pediatric victims of chemical terrorism is an especially difficult challenge. In addition to the obvious physiologic and anatomic differences compared to adults (Table 61.1), there are important psychological and behavioral differences that put children at risk (Rotenberg and Newmark, 2003). Anecdotal reports have claimed that children are likely to be the first to manifest symptoms, to develop more severe manifestations, and to be hospitalized for other related illnesses. In fact, it is anticipated that children will be overrepresented among the initial index cases in a mass civilian exposure to toxic chemicals. Children have many characteristics that make them vulnerable to toxic exposures. The smaller mass of a child automatically reduces the dose of toxic agents needed to cause observable or lethal effects. Studies involving organophosphates (OPs), compounds related to nerve agents, have shown greater vulnerability in immature animals. Some OPs produce the same degree of lethality in juveniles at a fraction of the dose producing lethality in the adult (Rotenberg and Newmark, 2003). Children exhibit an exceptional vulnerability to both the acute and chronic effects of chemicals and are disproportionately susceptible in comparison with adults. The increased toxicity seen in children compared to adults from various routes of exposure can be attributable to a wide variety of factors (shown in Exhibit A). These unique anatomical and physiologic considerations described below cause the rates of absorption, distribution, metabolism, and excretion of toxic chemicals/drugs to differ in children with respect to adults.

B. Respiratory Vulnerability

Inhaled doses in young children may be greater than adults. Some studies have demonstrated a two-fold increase in respiratory tract exposure per unit surface area as compared to adults (Bennett and Zeman, 1998). Deposition of fine particles is higher in young children (ages 7 to 14) relative to adults when the data are normalized by lung surface area (Bennett and Zeman, 1998) and an even greater deposition has been modeled for younger age children (Martonen *et al.*, 2000). The higher respiratory rate and minute volumes per respiratory surface area of a child means that they will inhale a greater dose of a toxic chemical vapor (Rotenberg and Newmark, 2003). Also, children can become intoxicated simply through breathing air that is closer to the ground. Many toxic chemicals display a high vapor density, causing them to distribute closer to the ground (CSMC, 2003). This may lead to greater toxicity for a child compared to an adult. In addition, children have less endurance than adults in the use of their respiratory accessory muscles, putting them at risk for respiratory failure.

Children are especially susceptible from toxic chemicals due to their unique airway anatomy (Figure 61.2). These differences include a greater degree of subglottic narrowing, diminished airway diameter, tendency for nose-breathing, and large tongue size relative to the mouth (Rotenberg and Newmark, 2003). OP nerve agents induce bronchospasm and bronchoconstriction during a cholinergic crisis. In comparing the effect of nerve agent on adult and pediatric airways, Figure 61.2 illustrates that a similar change in airway diameter results in a greater percent increase of airway resistance in children. In addition, copious glandular secretions during a cholinergic crisis may further restrict airflow through an already narrow airway. Therefore, children are at higher risk for toxicity from inhalational chemical exposure.

C. Volume Status Vulnerability

The circulatory system of children can be severely affected by chemical attacks (Rotenberg and Newmark, 2003).

TABLE 61.1. Summary chart of pediatric vulnerabilities and implications for clinical management

Unique vulnerability in children	Implications and impact from chemical toxicity
Body composition	
• Larger BSA/body mass • Lower total lipid/fat content	• Greater dermal absorption • Less partitioning of lipid soluble components
Volume status	
• More prone to dehydration • Chemical agents lead to diarrhea and vomiting	• Children can be more symptomatic and show signs of severe dehydration
Respiratory	
• Increased basal metabolic rate/greater minute volume	• Enhanced toxicity via inhalational route
Blood	
• Limited serum protein binding capacity • Greater cutaneous blood flow	• Potential for greater amount of free toxicant and greater distribution • Greater percutaneous absorption
Skin	
• Thinner epidermis in preterm infants • Greater cutaneous blood flow	• Increased toxicity from percutaneous absorption of chemical agents
Organ size/enzymatic function	
• Larger brain/body mass • Immature renal function/lower renal function • Immature hepatic enzymes	• Greater CNS exposure • Slower elimination of renally cleared toxins, chemicals and metabolites • Decreased metabolic clearance by hepatic phase I and II reactions
Anatomical considerations	
• Short stature: breath closer to ground where aerosolized chemical agents settle • Smaller airway • Greater deposition of fine particles in the upper airway • Higher proportion of rapidly growing tissues	• Mustard significantly affects rapidly growing tissues • Exposure to chemicals can have significant impact on bone marrow, developing CNS • Increased airway narrowing from chemical agent-induced secretions
CNS	
• Higher BBB permeability • Rapidly growing CNS	• Increased risk of CNS damage
Miscellaneous	
• Immature cognitive function • Unable to flee emergency • Immature coping mechanisms	• Inability to discern threat, follow directions, and protect themselves • High risk for developing PTSD

EXHIBIT A

Anatomical and Physiological Considerations Unique to Children

- differences in anatomy
- allometric scaling factors (e.g. increased surface area-to-volume ratio)
- cardiovascular status
- permeability of the pediatric blood–brain barrier (BBB)
- dermatologic factors (e.g. increased cutaneous blood flow) (Fluhr *et al.*, 2000; Simonen *et al.*, 1997)
- increased skin pH (Fluhr *et al.*, 2004; Behrendt and Green, 1958)
- plasma protein binding
- volume of distribution (V_d)
- organ size and maturity
- pharmacokinetic maturity (e.g. metabolic differences) (Fairley and Rasmussen, 1983)

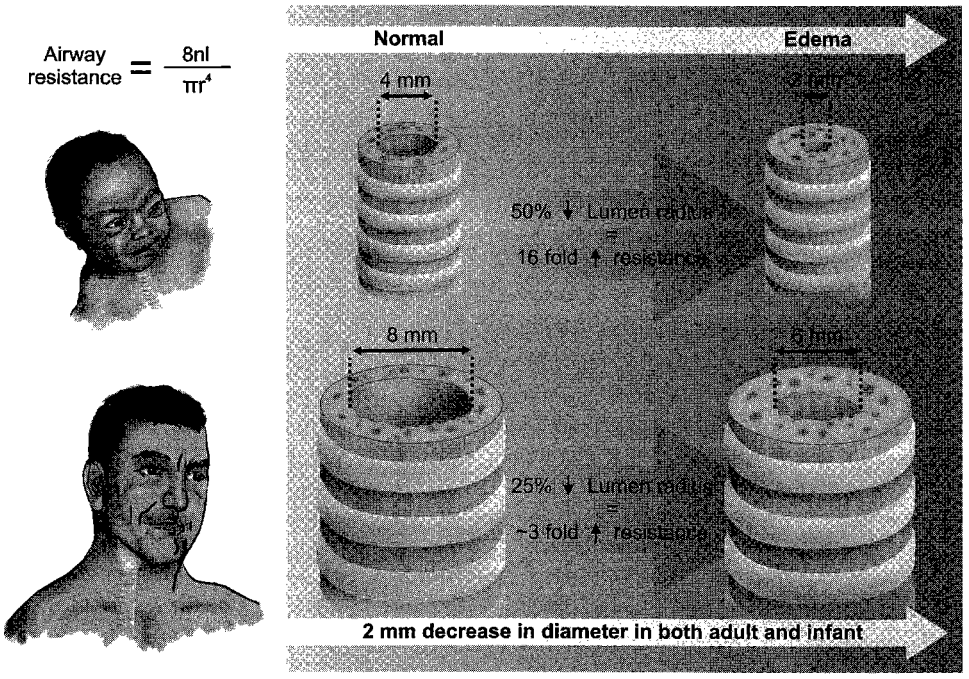

FIGURE 61.2. Comparison of pediatric and adult airways. The most important factor to consider in pulmonary toxicity from cholinesterase inhibition is the airway resistance through the conducting portion of the respiratory system. Airflow from the trachea and mainstem bronchi to the small bronchioles can be characterized as airflow through a series of straight tubes or laminar flow (West, 1995; Guyton and Hall, 2005). Poiseuille's law provides a relationship between flow rate and radius of the tube ($F = P\pi r^4/8nl$), where n is the coefficient of viscosity, P is the pressure difference across the length l of the airway section, r is the radius of the airway, and F is the airway flow rate. Since the resistance to flow R is driving pressure P divided by flow F, using the analogy of Ohm's law, the following relationship for airway resistance R can be derived ($R = 8nl/\pi r^4$). The effect of a 2 mm change in airway diameter on airway resistance is illustrated for both an infant and an adult. *Bottom panel* (adult scenario): a 2 mm reduction in the airway radius as a result of nerve agent-induced bronchoconstriction results in a 25% reduction and a corresponding increase in airway resistance by approximately three-fold. *Top panel* (infant scenario): a similar reduction in a child decreases the airway lumen by 50% and increases airway resistance by 16-fold. Illustrations are copyright protected and printed with permission by Alexandre M. Katos.

Children have lower fluid reserves, and small fluid volume losses can cause significant effects. For example, a 5 kg child, experiencing severe dehydration (15% body weight loss), loses 750 ml of fluid. A significant loss of fluid from the gastrointestinal tract as a result of chemical-induced glandular secretions can affect intravascular volume. Also, children are more prone to vomiting and diarrhea than adults. Therefore, children may dehydrate faster during a chemical event (CSMC, 2003).

D. Neurological Vulnerability

The immature central nervous system (CNS) of children can lead to greater toxicity (Rotenberg and Newmark, 2003). Toxic agents can often transverse the immature blood–brain barrier in children. Infants and children are at greater risk of seizures than adults. This is concerning because seizures are common in cases of moderate to severe nerve agent intoxication. Infants are at the highest risk of toxicity due to their susceptibility to imbalances of neurotransmitter systems. Prolonged seizures, or status epilepticus, can cause neuronal injury and deficits of normal brain development in children.

E. Dermatologic Vulnerabilities

Barrier thickness, cutaneous blood flow, surface to volume ratio, temperature, hydration, and skin pH are important factors to consider in the assessment of pediatric dermatological vulnerabilities. The skin of newborns, while appearing vulnerable, has the same histologic features of adult skin with some differences including immaturity of collagen, hair follicles, and sebaceous glands. While newborns and young children are often described as having thinner skin than adults, the stratum corneum, the most superficial layer of the skin, is thinner in premature infants compared to full-term infants, children or adults (Rutter and Hull, 1979; Harpin and Rutter, 1983; Nopper *et al.*, 1996). The skin of a child, however, does not differ significantly compared to adults as evidenced by similar measurements of skin physiological parameters (e.g. transepidermal water loss, skin pH, and stratum corneum capacitance and conductance) (Fluhr *et al.*, 2000). Children 3 months old have the same abdominal skin stratum corneum thickness as 11 year olds and adults (Fairley and Rasmussen, 1983).

Moreover, children have larger surface area-to-volume (mass) ratios, resulting in greater absorption of chemicals.

The skin surface area of infants and toddlers is very large compared to their body weight. An increase in the surface area-to-body weight ratio increases their potential absorption to dermal exposures of chemicals. For instance, a typical infant weighs a fraction (1/20) of an adult 70 kg male, but an infant's surface area is only 1/8 as great. The total skin surface area that is exposed per kg of body weight is therefore 2.5 times higher for infants than adults (Lynch and Thomas, 2004). Burns with extensive skin loss, as seen with certain chemical exposures, can cause significant water loss and toxicity in children (Lynch and Thomas, 2004). Despite the few prospective scientific studies on skin vulnerability in the pediatric population, it can be summarized that the thin, immature skin of preterm infants and the unique dermatological properties of children put them at higher risk for toxicity from percutaneous chemical exposure (CSMC, 2003).

F. Plasma Protein Binding, Volume of Distribution, and Organ Maturity

Children may be at an increased risk of chemical toxicity due to having lower levels of plasma proteins. One factor affecting the amount of free chemical/drug in the circulation is the fraction bound to plasma protein. Neonates have a low protein binding capacity for albumin and alpha-1-glycoprotein (Besunder *et al.*, 1988; Kearns and Reed, 1989; Clewell *et al.*, 2002) and a decreased ability to conjugate and excrete bilirubin, which binds to plasma proteins. This can lead to a smaller pool of available protein binding sites in plasma (Ginsberg *et al.*, 2004). A lower serum protein binding capacity equates to a greater fraction of free chemical available in the circulation and therefore increased toxicity.

The volume of distribution or V_d (liters per kg body weight) of chemicals/drugs is an important factor to consider in pediatrics. Because of the expanded water content in early life (newborns and infants), water soluble chemicals may tend to have a larger volume of distribution. Toxic lipophilic agents, on the other hand, will be decreased in their partitioning to fat because of the lower body lipid content in young children compared to older children and adults (Kearns and Reed, 1989; Clewell *et al.*, 2002; Morselli, 1989). It can be argued that due to lower fat stores, lipophilic agents such as nerve agents will reach higher concentrations in the plasma, leading to an increased risk of chemical toxicity.

Another factor affecting tissue distribution of chemicals in children is organ size per body weight. The brain is disproportionately large in young children. This fact, combined with an immaturity and permeability of the BBB in young children, leads to higher brain concentrations of some chemicals and the potential for enhanced neurotoxicity (Saunders *et al.*, 2000). Liver mass per body weight is greatest in the early postnatal period and other tissues (liver, kidney, lung, and brain) undergo rapid growth during the first 2 years of life (NRC, 1993). These organs are at increased risk for toxicity in children due to their disproportionately larger size per body weight.

Organ maturity in the pediatric population is another factor affecting clearance of toxic agents and therapeutics. In particular, renal clearance is diminished in children compared to adults. Glomerular filtration rate and transporter (secretory) systems in the proximal convoluted tubule are decreased at birth (Kearns and Reed, 1989; Morselli, 1989). In addition, cardiac output, while higher in children, has a lower percentage reaching the kidneys in early life (Ginsberg *et al.*, 2004). This will tend to decrease renal clearance even more, leading to even greater plasma levels of toxic agent. A consequence of immature kidney function and reduced clearance in children can be seen with nerve agents since the parental forms of nerve agents and their metabolites undergo hydrolysis with predominantly renal elimination.

One might consider that renal clearance is faster due to allometric scaling differences in children compared to adults. According to the rules of allometric scaling, smaller organisms have greater respiratory rates, cardiac output, nutrient and oxygen demands, and basal metabolic rates compared with larger organisms. This appears true for children because respiratory rate, cardiac output, and liver mass are greater per body weight than adults. However, faster metabolic rates are not seen in neonates because of immaturity of hepatic enzymes and reduced hepatic clearance, leading to a prolonged toxic agent/drug half-life and longer duration of action.

G. Metabolic Vulnerability

Children are unable to detoxify toxic agents as efficiently as adults because they have less mature metabolic systems (Rotenberg and Newmark, 2003). In particular, phase I oxidative systems, phase II conjugating systems, and miscellaneous other systems (e.g. serum esterases, hydrolases, dehydrogenases) are all immature in children compared to adults. Neonates and children up to 1 year are most affected in their maturing enzymatic function with the greatest effect seen in the first 2 months of life. This leads to slower metabolic clearance of many drugs, toxic chemicals, and activated metabolites, leading to significant toxicity in this age group (Ginsberg *et al.*, 2004). In addition, several authors have reported a reduced activity of acetylcholinesterases, pseudocholinesterases, and arylesterases (paraoxonase) in premature and full-term newborns (Stead, 1955; Lehmann *et al.*, 1957; Augustinsson and Brody, 1962; Ecobichon and Stephens, 1973). These levels do not reach adult levels until 1 year of age (Morselli, 1976). In addition, newborns possess levels of paraoxonase, the enzyme that detoxifies organophosphate pesticides, that are half of those found in the general adult population (Rotenberg and Newmark, 2003). Other studies suggest that newborns have paraoxonase levels four-fold lower and activities three times lower than in their mothers (Holland *et al.*, 2006).

H. Traumatic Injury Vulnerability

Another special challenge to managing pediatric patients is the fact that trauma and injury often accompany chemical attacks (Abraham *et al.*, 2002). Chemical exposures are often dispersed through explosive devices. Traumatic injury patterns differ in children compared to adults. Due to the smaller size of children, multiple trauma occurs more frequently. Compared to adults, children often sustain more head trauma due to their relatively large head size and weaker supportive musculature. Also, their more compliant skeletal system provides less protection to internal organs, leading to greater internal injuries without overlying fractures.

I. Neurobehavioral Vulnerability

Immature cognitive function can put children at risk during a chemical attack (Rotenberg and Newmark, 2003). Children lack the ability to discern threat, to protect themselves, or to follow directions. Infants, toddlers, and young children do not have the motor skills to flee from the site of an incident (CEH/CID, 2000). This can adversely impact their avoidance of a contaminated area and decontamination in the event of exposure. During decontamination, procedures for children who have been separated from their caregivers must be taken into consideration. Without guidance, children may not be able to follow directions for the decontamination process (Wheeler and Poss, 2003).

J. Psychological Vulnerability

Children have fewer coping skills when sustaining or witnessing injury such as parental or sibling death (Henretig *et al.*, 2002b). These events can produce either short- or long-term psychological trauma. It is not unusual for children involved in attacks to suffer from post-traumatic stress disorder (PTSD) related to what they have experienced (CEH/CID, 2000; ARC, 2002). During the management of a chemical event, there are certain behaviors that make the management of children difficult. Children are often influenced by the emotional state of caregivers, requiring providers to remain calm. Also, fear or discomfort may cause children to disobey or act out against providers of care (see Table 61.1) (Blaschke *et al.*, 2003).

Even beyond the behavior of children, there are other barriers to emergency management. The high pressure hoses and cold water that are used to decontaminate victims can expose children to significant additional risk (CSMC, 2003). Use of these items can result in hypothermia and skin damage. Also, emergency care providers often need to wear bulky full protective suits when treating victims. These suits make it difficult to treat very small children who might need intricate procedures such as blood draws. One constant challenge that is consistent with the management of children is the lack of pediatric formulations of specific therapeutics (e.g. autoinjectors containing oxime). Antidotes for chemical agents are often not available in ready-to-administer pediatric dosages, although some progress has been made. In the event of a true chemical event, there is a risk that pediatric centers would be overwhelmed and the ability to expand the number of pediatric hospital beds may be limited (CEH/CID, 2000). Finally, most health care workers are not fully aware of the management or presentation of toxic signs and symptoms from chemical agents. This problem is exacerbated when children typically present differently than adults.

K. Other Vulnerabilities

In addition to the vulnerabilities listed above, there are other factors that can put children at greater risk for toxicity from chemical agents attacks. For instance, the fluid and food intakes of children differ significantly from adults with greater water and milk consumption per weight. Children ingest about 100 ml/kg per day of water compared to the 40–60 ml/kg per day ingested by adults. If water or milk supplies become contaminated, children would feel a greater impact than adults. Also, the diets of children include greater consumption of foods that can be contaminated such as fruits and vegetables (CEH/CID, 2006).

L. Medical Response Vulnerability

Due to the myriad of factors outlined above that make the management of pediatric chemical exposures challenging, it is not surprising that health care practitioners often do not have the knowledge or are not sufficiently trained to handle a mass influx of pediatric casualties. This deficiency was clearly documented in a recent study done by Schobitz *et al.* (2008), where pediatric and emergency medicine residents were tested on the medical management of pediatric victims of biological and chemical terrorism (Schobitz *et al.*, 2008). A test containing essential content was developed and validated by experts. This test was given to volunteer residents and was readministered 5 months after a lecture on the content. The 34 pediatric residents and 15 emergency medicine residents who took the exam scored a median of 65% and 73%, respectively. The authors investigated the benefit of the lecture and found that the 16 residents who attended the lecture and completed the post-test achieved a median score of 70%. For the 20 residents who did not attend the lecture, but completed the post-test, a median score of 66.6% was recorded. The authors concluded that there are significant knowledge deficits among pediatric and emergency medicine residents in their abilities to handle pediatric victims of biological and chemical terrorism. A suggestion was made to incorporate educational curriculum on preparedness into residency curriculums (Schobitz *et al.*, 2008).

EXHIBIT B (Pediatric Case History) – Nerve Agents

Nerve Agent Exposure in Town of Nazhmar, Iran

One victim of the March 22, 1988 attack on the village of Nazhmar was a young child with unreported age and weight. He presented immediately with marked miosis and was comatose. Breathing was irregular and foamy secretions were evident protruding from his mouth and nose. The patient was working very hard to breathe and noted to be using his accessory muscles of respiration. Wheezing was obvious on auscultation, and he showed obvious difficulty on exhalation. Upon suction removal of oral and nasal secretions, the patient was noted to have progressively rigid extremities such that finding venous access became difficult. The secretions were noted to become bloody. Over a 15 min period, a total of 7.5 mg atropine was administered during three treatments. The patient was noted to improve with eye opening, moaning, and two-word phrases. As his muscle tone decreased, his breathing improved, but wheezing was still evident. The child was decontaminated after treatment and subsequently discharged after an hour. At the time of discharge, secretions were not completely dried up, but his pupils were fully dilated and reactive to light.

(*ref:* Foroutan, 1998c)

V. EFFECTS OF SPECIFIC AGENTS

A. Nerve Agents

1. Introduction

Nerve agents pose a real threat to our unprotected civilian population. They can quickly incapacitate those who are exposed and can lead to mortality if not recognized and treated promptly. The toxicity of these agents can be enhanced in children due to pediatric vulnerabilities. Also, it is important to recognize the different ways children may present with toxicity compared to adults.

The major nerve agents are the G-series (tabun, sarin, cyclosarin, soman) and V-series (VX) compounds. These agents are clear, colorless, tasteless, and in most cases, odorless. They have been demonstrated to penetrate normal clothing and skin. Also, these agents are highly toxic as evidenced by the fact that as little as 10 mg of VX on the skin is considered to be an LD_{50} in adults (Rotenberg and Newmark, 2003). In addition, these agents produce toxicity rapidly compared to biological agents. Most G-series nerve agents are highly volatile, and can be dispersed into aerosols that are inhaled by victims. One of the G-series agents, sarin, is volatile and may sink close to the ground (in undisturbed air) where children breathe. Nerve agents may also be disseminated in liquid form. Treatment for dermal exposure begins with rapid topical decontamination.

Although our military experience managing toxicity from nerve agent exposure is limited, exposures to related chemicals such as the OP class occur commonly each year in the USA. In 2006, there were a total of approximately 5,400 OP exposures across the USA (Bronstein *et al.*, 2007). OPs, such as malathion, are commonly used as pesticides. OP toxicity manifests in a similar fashion as toxicity from nerve agents; however, this chemical class is considerably less toxic. One case series of 16 children who experienced poisonings with OPs confirmed that pediatric patients present with toxicity differently than adults (Lifshitz *et al.*, 1999). These children often did not manifest the classic muscarinic effects (such as salivary secretions and diarrhea) seen in adults.

2. Mechanism of Toxicity

Nerve agents cause toxicity by inhibiting esterase enzymes, especially acetylcholinesterase (AChE) (Rotenberg and Newmark, 2003). When nerve agents bind to AChE, they prevent hydrolysis of acetylcholine (ACh). When ACh accumulates in the synaptic space of neurons, this leads to overstimulation of muscarinic and nicotinic receptors. This overstimulation is often termed "cholinergic crisis". Also, it is important to note that the nerve agent–AChE bond undergoes a reaction called "aging" (Dunn and Sidell, 1989). Once this process is complete, the enzyme becomes irreversibly inactivated. This aging process dictates the need for prompt therapy to prevent irreversible toxicity.

3. Clinical Presentation

The signs and symptoms of a cholinergic crisis can be remembered using the mnemonic BAG the PUDDLES (Figure 61.3); these range in severity from lacrimation and urination to seizure activity (Rotenberg and Newmark, 2003). The manifestations of cholinergic crisis seen in a particular individual depend on the dose and route of exposure, as well as the duration of exposure. If death occurs from nerve agents, it is primarily attributed to respiratory failure. Nerve agents affect the respiratory system by causing central apnea, flaccid neuromuscular paralysis, bronchoconstriction, and profound glandular secretions (Hilmas *et al.*, 2006).

Children present a clinical picture that can be very different to that observed in adults. Children in cholinergic crisis may not necessarily manifest with miosis (constriction of pupils) (Rotenberg and Newmark, 2003). In fact, one case series demonstrated absence of miosis in 43% of pediatric victims. Studies involving pediatric exposure to organophosphates have suggested the appearance of isolated CNS effects (such as stupor, coma) in the absence of peripheral muscarinic effects. Pediatric victims of OP intoxication display significant muscular weakness and hypotonia in the absence of glandular secretions in 70–100% of cases involving moderate to severe levels of exposure (Rotenberg and Newmark, 2003). For adults, a presentation of central

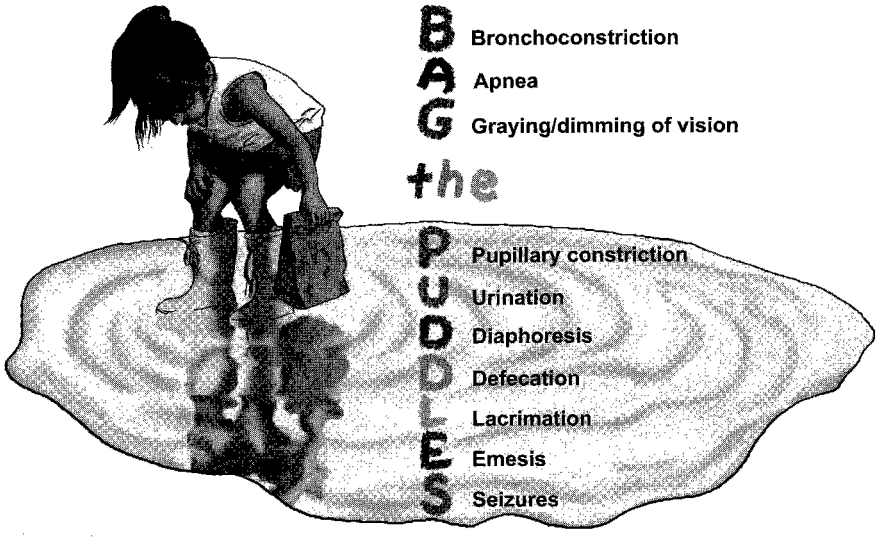

FIGURE 61.3. Helpful mnemonic for cholinergic crisis (BAG the PUDDLES). Illustrations are copyright protected and printed with permission by Alexandre M. Katos (Rotenberg and Newmark, 2003).

intoxication (weakness and hypotonia) from OPs without peripheral muscarinic signs and symptoms would be extremely atypical.

Unfortunately, there are no data on the long-term effects of nerve agent poisoning in children, and the effects must be extrapolated from what has been discovered in the adult population (Rotenberg and Newmark, 2003). Surveillance studies performed on victims of the sarin attacks in Japan revealed a wide range of sequelae, such as continued respiratory problems, vision disturbances, headache, and fatigue. Neuropsychiatric problems were also reported as a delayed effect.

4. Laboratory Findings

Use of cholinesterase levels is limited, especially for confirmation of exposure (Rotenberg and Newmark, 2003). Treatment should not be delayed for these levels to return. Levels should be used after exposure only to confirm diagnosis (after treatment has begun), to monitor recovery, or for forensic investigation.

5. Pediatric Vulnerability

Children have several vulnerabilities, putting them at increased toxicity from this class of chemical agents. A child's smaller mass alone reduces the dose needed to cause symptoms or lethality. For volatile nerve agents, children are especially at risk for respiratory toxicities due to their anatomic differences compared to adults. Their smaller airways can become compromised by the large amount of secretions and the bronchospasm caused by the agents. Also, a greater dose of nerve agent will be inhaled in children due to their higher respiratory rate and minute volumes.

6. Treatment

The overall treatment approach to nerve agent exposure focuses on airway and ventilatory support, aggressive use of antidotes (atropine and pralidoxime), prompt control of seizures, and decontamination as necessary (Henretig, 2002a). Atropine is used for its anti-muscarinic effects, and oxime is used to reactivate AChE. The combination of atropine and pralidoxime chloride (2-PAM Cl) is recommended for the prompt treatment of all serious cases. The timing of atropine and 2-PAM Cl administration is critical. In short, the faster these antidotes are given, the better the outcome. Oxime therapy is rendered ineffective if given after the enzyme aging process has been completed (Dunn and Sidell, 1989). This fact has led to the use of autoinjectors because of their ability to rapidly administer intramuscular doses of these medications. However, there are no currently Food and Drug Administration (FDA)-approved pediatric autoinjectors for 2-PAM Cl. Other administration routes and methods include intravenous (IV) or intraosseous (IO) for atropine and slow IV or continuous infusion for 2-PAM Cl. Data show that peak plasma concentrations of medications administered from autoinjectors are achieved in less than 5 min versus 25 min for intramuscular (IM) administration using a needle and syringe (Rotenberg and Newmark, 2003). The mainstay of adult therapy includes the use of autoinjector technology containing atropine and 2-PAM. Recently, Meridian Medical Technologies™ has developed and received FDA approval for a dual-chambered autoinjector called the ATNAA (Antidote Treatment Nerve Agent Autoinjector) for the military and Duodote™ for civilian emergency medical technicians and first responders (see Figure 61.4). Meridian also produces the older Mark I™ kit (Figure 61.5) which is composed of separate autoinjectors for atropine and 2-PAM.

These products are provided by Meridian Medical Technologies, which has partnered with the US Department of Defense to be the only FDA-approved supplier of nerve agent antidotes. The Mark I™ kit and the single autoinjector devices deliver 600 mg of 2-PAM Cl and 2 mg of atropine (AtroPen®) in seconds. This kit was developed originally

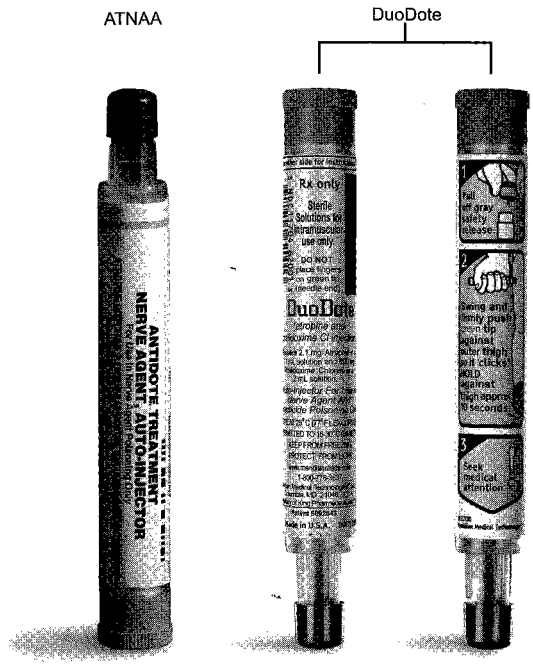

FIGURE 61.4. ATNAA and Duodote™. Photo reproduced with permission from Meridian Medical Technologies™.

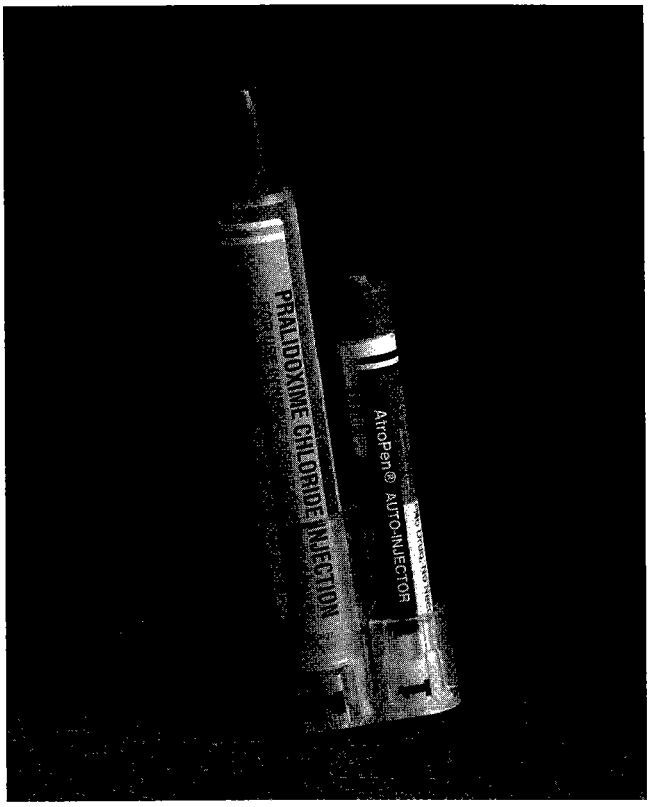

FIGURE 61.5. The MARK 1™ kit. Photo reproduced with permission from Meridian Medical Technologies™.

for administration to soldiers, not for children, and with the approval of the Duodote system, the Mark I kit will most likely become antiquated. The autoinjector technology incorporates a spring-loaded needle to disperse medication in an "all-or-nothing" fashion. It is impossible to give partial doses of an autoinjector for children. Drug dosing of atropine and 2-PAM Cl in pediatrics is primarily weight based, so a standard dose cannot be used. Pediatric versions of the Mark 1™ kit are available overseas but are not currently available in the USA (PEAP, 2004). In June 2003, the FDA approved pediatric doses of the AtroPen® (atropine autoinjector) to respond to the lack of pediatric specific therapy (Meadows, 2004). Meridian's AtroPen is now available in four dosages, 0.25 mg, 0.5 mg, 1 mg, and 2 mg (Figure 61.6). The 0.25 mg dose should be used for infants weighing less than 7 kg, the 0.5 mg treats patients weighing 7–18 kg, the 1 mg treats patients weighing 18–41 kg, and the 2 mg dose should be used for children/adolescents who weigh more than 41 kg. The needle length for these autoinjectors is 0.8 inches, with a needle gauge of 22. Administration technique of autoinjectors in children is displayed in Figure 61.7. Since the AtroPen® delivers only atropine and not 2-PAM Cl, there continues to be a limitation to the prompt treatment of children. This fact has caused groups such as the pediatric expert advisory panel from the National Center for Disaster Preparedness to recommend the use of the Mark 1™ kit before use of the AtroPen (PEAP, 2004). A table of how to use the Mark

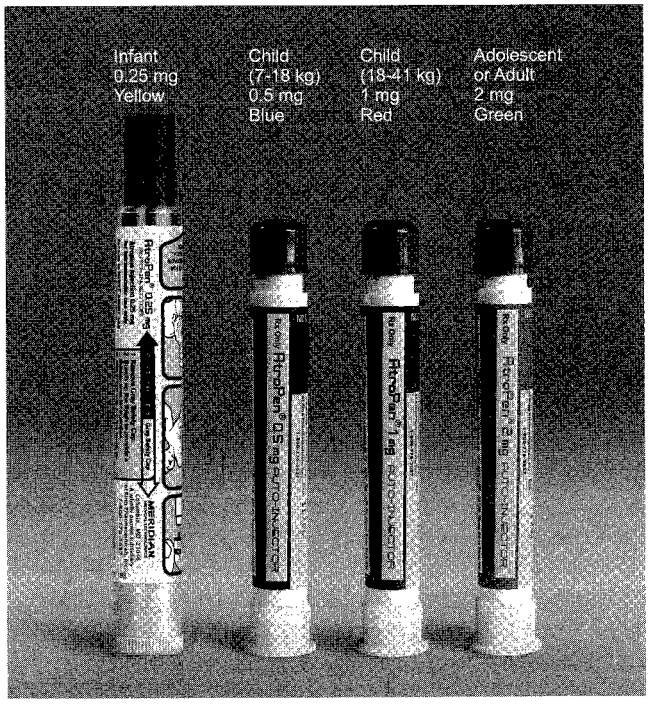

FIGURE 61.6. The Atropen® pediatric autoinjectors. Dose sizes: 0.25 mg – infant, 0.5 mg – child (7–18 kg), 1 mg – child (18–41 kg), 2 mg – adolescent/adults. Photograph reproduced with permission from Meridian Medical Technologies™.

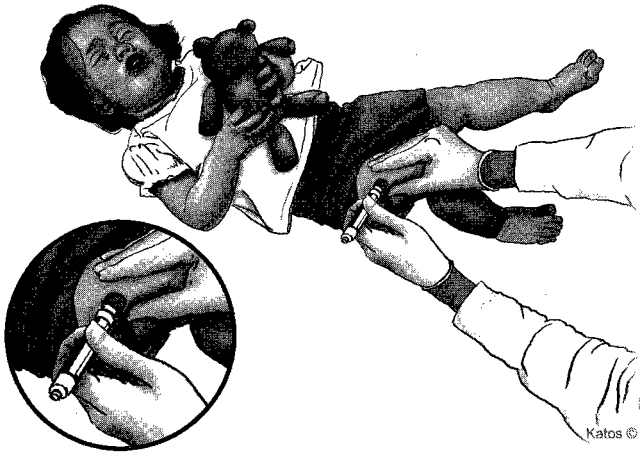

FIGURE 61.7. Technique for using Atropen® pediatric autoinjector.

1 kit for children is displayed in Table 61.2. The use of adult dose-based autoinjectors in children has been addressed. Amitai *et al.* (1992) reviewed 240 instances of accidental pediatric atropine injections using adult dose-based autoinjectors. A low incidence of toxicity was found, with no seizures, arrhythmias, or death. Subsequently, several pediatric guidelines have suggested adult-dose atropine and 2-PAM Cl autoinjectors can be safely used in children larger than 13 kg and inserted to 0.8 inches.

Administration of atropine and 2-PAM Cl must be done cautiously (Rotenberg and Newmark, 2003). Atropine can cause increased heart rate, dry mouth and skin, and near vision can be affected for up to 1 day. Due to the fact that sweating is prevented, elevated temperatures and heat stress may be observed. 2-PAM Cl can cause double or blurred vision and dizziness (Anon, 2002). Doses must be reduced with renal insufficiency. If a medication is given too quickly as an intravenous injection, laryngospasm and rigidity can occur. Higher doses can cause hypertension while lower doses can cause mild electrocardiogram changes (Rotenberg and Newmark, 2003).

Although benzodiazepines are not considered to be an antidote, their use in the treatment of nerve agent exposures is critical (Rotenberg and Newmark, 2003). Status epilepticus can often occur as the nerve agent crosses the blood–brain barrier and causes irritation. Benzodiazepines are the only effective agents that have been proven to treat nerve agent-induced seizures. This group of medications should be used for both prevention and treatment. It is recommended that if more than one organ is impaired, there is impaired consciousness, or muscle twitching, benzodiazepines should be quickly administered. In choosing a specific medication, various agents can be used. Our military department uses the medication diazepam that is administered as an autoinjector (Figure 61.8). In Israel, there is a move towards using midazolam for their population. Some physicians are recommending the use of lorazepam in the pediatric population. Regardless of which medication is used, repeat doses may be needed. For the pediatric population, benzodiazepines should be considered if there is any suspicion of seizure activity. Nonconvulsive status and subtle seizures are common in infants and children, making it difficult for health care providers to recognize nerve agent toxicity.

For each of the medications used to treat nerve agent toxicity, there is weight-based dosing recommendations for pediatric patients. The exact dose to utilize for a specific patient will depend on two critical factors: the severity of the exposure and the weight or age of the patient. Pediatric dosing recommendations for medications used to treat mild to moderate nerve agent exposures are displayed in Table 61.3. Dosing recommendations to treat severe nerve agent exposures are displayed in Table 61.4.

7. Perioperative Care of Children with Nerve Agent Intoxication

As mentioned earlier, it is not uncommon for chemical exposures and trauma to occur at the same time, necessitating the need for surgery. It is important to realize that many drugs used for perioperative management can exacerbate the side effects encountered with nerve agent exposure. Nerve agents can cause drug interactions with medications typically used for resuscitative efforts (Abraham *et al.*, 2001). Anesthetics, such as sodium penthothal and propofol, cause cardiac depression, an effect exacerbated by the excessive muscarinic activity induced by nerve agents. Doses of these drugs may need to be reduced. Use of volatile anesthetics may be preferable because they bronchodilate and reduce the need for nondepolarizing drugs. When nondepolarizing drugs are used, they are often reversed by the use of neostigmine, which affects AChE activity. Halothane should be avoided in infants because the

TABLE 61.2. Dosing of the Mark 1™ kit for children with severe, life-threatening nerve agent toxicity[a] (PEAP, 2004)

Approximate age	Approximate weight	Number of Mark 1™ kit autoinjectors to use	Atropine dosage range (mg/kg)	Pralidoxime dosage range (mg/kg)
3–7 yrs	13–25 kg	1	0.08–0.13	24–46
8–14 yrs	26–50 kg	2	0.08–0.13	24–46
>14 yrs	>51 kg	3	0.11 or less	35 or less

[a]If an adult MARK I kit is the only available source of atropine and pralidoxime, it should not be withheld from even the youngest child (i.e. <3 y.o.)

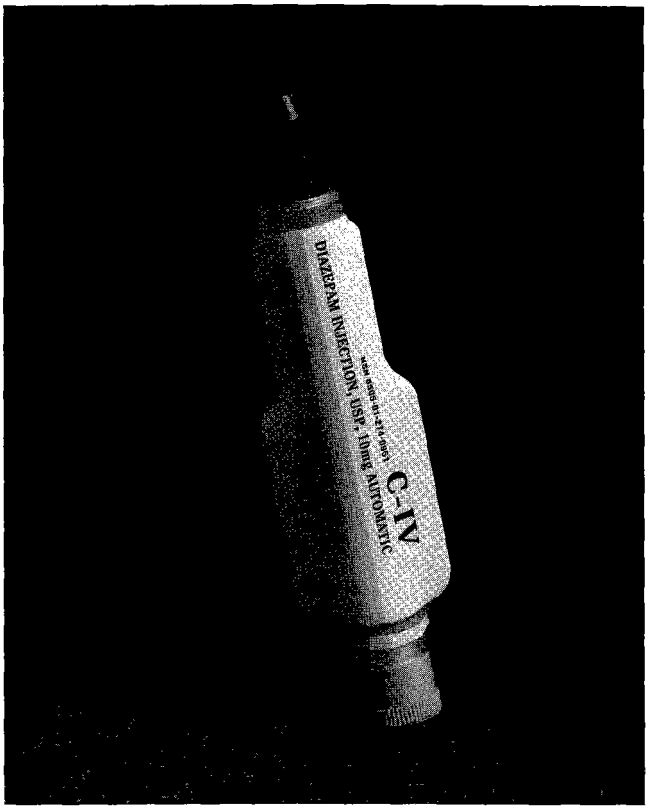

FIGURE 61.8. The diazepam autoinjector. Photograph reproduced with permission from Meridian Medical Technologies™.

cardiac side effects can be accentuated in the presence of nerve agents. Depression of the cardiovascular system by halothane may cause further bradycardia, hypotension, and reduction in cardiac output. In general, the use of muscle relaxants is not recommended in the setting of nerve agent toxicity. Nerve agents provide a depolarizing block and in the presence of inhibited AChE activity, drugs such as succinylcholine can have longer effects than expected (Rotenberg, 2003b).

Careful use of analgesia is important when caring for victims of nerve agent exposure (Abraham *et al.*, 2001). In general, opioids are considered safe to use because they do not act on the cholinergic system directly. However, some side effects of the drugs, such as histamine release and rare muscle rigidity, can cause difficulty in patient management. Careful dose titration and monitoring for side effects is critical. However, there is one opioid that can have an interaction with nerve agents. Remifentanyl, a potent opioid, contains an ester linkage susceptible to hydrolysis because it is partially metabolized by plasma cholinesterase. This is the same enzyme that is inactivated by nerve agents, resulting in a prolonged duration of action for remifentanyl. Therefore, use of remifentanyl in the post-operative care of nerve agent-exposed victims is not recommended as other analgesics are available (Rotenberg, 2003b). Compared to other chemical warfare agents, patients exposed to nerve agents pose unique challenges for medical and surgical management.

8. Summary

Nerve agent exposures must be handled quickly and efficiently. When children are exposed, it is important to remember that antidote dosing will be determined by the patient's weight and the severity of exposure. Progress has been made to provide pediatric-specific autoinjectors; however, since 2-PAM Cl is not yet available in a pediatric autoinjector form, it is possible to carefully use adult autoinjectors to manage pediatric patients.

B. Carbamates/Organophosphates

1. Introduction

Carbamates and OPs are chemicals that are often used as fungicides, insecticides, or pesticides and possess actions similar to nerve agents. These compounds are considered "weapons of opportunity" since their primary use is not by conventional militaries. In the USA, toxicity from these compounds is fairly rare. In 2006, there were approximately 1,200 cases of carbamate exposures and 1,500 organophosphate exposures documented for children 19 years old and younger (Bronstein *et al.*, 2007). Although there were a few fatalities reported in 2006 from these substances, these fatalities occurred only in older individuals.

In general, the toxicity of these compounds resembles that of nerve agents, but is less severe. Pediatric cases of toxicity reported in the literature are often due to accidental poisoning when a young child ingests chemicals placed in unsecured or unlabeled containers. Exposure also can come by consuming foods that have been sprayed with pesticides. Most of the literature on pediatric toxicity from these agents includes retrospective reviews coming out of Israel, where use of these substances as a pesticide for the home and agriculture is common. A retrospective review of 37 cases from the USA has also been published (Zwiener and Ginsburg, 1988).

2. Mechanism of Toxicity

These compounds inhibit the hydrolysis of the neurotransmitter acetylcholine by the enzyme acetylcholinesterase within the mammalian nervous system (Zwiener and Ginsburg, 1988). This inhibition causes acetylcholine levels to rise, thus causing cholinergic hyperstimulation at muscarinic and nicotinic receptors. There are important differences in the way carbamates and OPs bind to acetylcholinesterase as well as their abililty to affect the CNS. Carbamates are reversible inhibitors of cholinesterase enzymes. Carbamates create a reversible bond to the cholinesterase enzyme through carbamylation which can spontaneously hydrolyze, reversing toxicity. Carbamate poisoning produces toxicity similar to that of OPs; however, the toxicity is usually of a shorter duration and less severe in nature (Lifshitz *et al.*, 1994). In contrast, OPs inhibit cholinesterase via an irreversible bond of phosphate radicals

TABLE 61.3. Management of mild/moderate nerve agent exposures (Rotenberg and Newmark, 2003; Anon, 2002)

		Management			
		Antidotes[a]		Benzodiazepines (if neurological signs)	
Nerve agents	Severity of symptoms	Age	Dose	Age	Dose
Tabun, sarin, cyclosarin, soman, VX	**Mild/moderate symptoms** • localized sweating • muscle fasciculations • nausea • vomiting • weakness/floppiness • dyspnea • constricted pupils • blurred vision • rhinorrhea • excessive tears • excessive salivation • chest tightness • stomach cramps • tachycardia or bradycardia	Neonates and infants <6 mo	**Atropine** 0.05 mg/kg IM/IV/IO to max 4 mg or 0.25 mg AtroPen® and **2-PAM** 15 mg/kg IM or IV slowly to max 2 g/h	Neonates	**Diazepam** 0.1–0.3 mg/kg/dose IV to a max dose of 2 mg OR **Lorazepam** 0.05 mg/kg slow IV
		Infants (6 mo–4 yrs)	**Atropine** 0.05 mg/kg IM/IV/IO to max 4 mg or 0.5 mg AtroPen® and **2-PAM** 25 mg/kg IM or IV slowly to max 2 g/h	30 days–5 yrs	**Diazepam** 0.05–0.3 mg/kg IV to a max of 5 mg/dose OR **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
		Children (4–10 yrs)	**Atropine** 0.05 mg/kg IV/IM/IO to max 4 mg or 1 mg AtroPen® and **2-PAM** 25–50 mg/kg IM or IV slowly to max 2 g/h	5 yrs and older	**Diazepam** 0.05–0.3 mg/kg IV to a max of 10 mg/dose OR **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
		Adolescents (>10 yrs) and adults	**Atropine** 0.05 mg/kg IV/IM/IO to max 4 mg or 2 mg AtroPen® & **2-PAM** 25–50 mg/kg IM or IV slowly to max 2 g/h	Adolescents and adults	**Diazepam** 5–10 mg up to 30 mg in 8 h period OR **Lorazepam** 0.07 mg/kg slow IV not to exceed 4 mg

[a]In general, pralidoxime should be administered as soon as possible, no longer than 36 h after the termination of exposure. Pralidoxime can be diluted to 300 mg/ml for ease of IM administration. Maintenance infusion of 2-P at 10–20 mg/kg/h (max 2 g/h) has been described. Repeat atropine as needed every 5–10 min until pulmonary resistance improves, secretions resolve, or dyspnea decreases in a conscious patient. Hypoxia needs to be corrected as soon as possible.

to the active esteratic site of the enzyme (Lifshitz *et al.*, 1999). Thus, the toxicity is more severe.

3. Clinical Presentation

OPs and carbamates have different receptor activities in the mammalian nervous system. OPs have effects on muscarinic and nicotinic receptors and can cause neurological effects in the CNS (Levy-Khademi *et al.*, 2007). Carbamates are thought to cause only parasympathetic muscarinic effects with limited nicotinic and CNS effects (Sofer *et al.*, 1989). However, there are case reports in children that have revealed the presence of CNS effects with carbamate exposures (de Tollenaer *et al.*, 2006). One pediatric case series stated that the signs and symptoms from carbamate poisoning were indistinguishable from OP exposures, with severe CNS depression with stupor and coma occurring in eight cases (Sofer *et al.*, 1989).

Muscarinic hyperstimulation leads to a clinical presentation of miosis, lacrimation, salivation, bradyarrhythmias, urinary incontinence, and intestinal hypermotility (Levy-Khademi *et al.*, 2007). Nicotinic hyperstimulation leads to fasciculations, weakness, and paralysis of skeletal muscles. CNS effects include depression and agitation with coma and seizures occurring in the most severe cases for adults. Generalized tonic–clonic seizures have been seen in several pediatric exposure cases reported in the literature (Zwiener and Ginsburg, 1988).

Additional toxicities that have been reported in the children include diarrhea, pulmonary edema which was associated with OP exposures but not carbamate exposures (Lifshitz *et al.*, 1999), acute pancreatitis, hyperglycemia (Weizman and Sofer, 1992), dyspnea, sweaty cold skin (Sofer *et al.*, 1989), respiratory distress or failure, lethargy, and tachycardia (Zwiener and Ginsburg, 1988).

4. Laboratory Findings

Key findings that have been reported include significant hypoxia, acidosis, and carbon dioxide retention (Sofer *et al.*, 1989). Also hyperglycemia, hypokalemia, and leukocytosis were observed in a case series of organophosphate exposures (Levy-Khademi *et al.*, 2007). A prospective study done on 17 children with typical organophosphate or carbamate poisoning looked at laboratory abnormalities that are associated with acute pancreatitis. Five of the patients (30%) had laboratory values consistent with pancreatitis with elevated immunoreactive trypsin, amylase, and serum

TABLE 61.4. Management of severe nerve agent exposures (Rotenberg and Newmark, 2003; Anon, 2002)

		Management			
		Antidotes[a]		Benzodiazepines (if neurological signs)	
Nerve agents	**Severity of symptoms**	**Age**	**Dose**	**Age**	**Dose**
Tabun, sarin, cyclosarin, soman, VX	**Severe symptoms** • convulsions • loss of consciousness • apnea • flaccid paralysis • cardiopulmonary arrest • strange and confused behavior • severe difficulty breathing • involuntary urination and defecation	Neonates and infants <6 mo	**Atropine** 0.1 mg/kg IM/IV/IO or 3 doses of 0.25 mg AtroPen® (administer in rapid succession) and **2-PAM** 25 mg/kg IM or IV slowly OR 1 Mark 1 kit (atropine + 2-PAM) if no other options exist	Neonates	**Diazepam** 0.1–0.3 mg/kg/dose IV to a max dose of 2 mg (PDH) OR **Lorazepam** 0.05 mg/kg slow IV
		Infants (6 mo–4 yrs)	**Atropine** 0.1 mg/kg IV/IM/IO or 3 doses of 0.5 mg AtroPen® (administer in rapid succession) and **2-PAM** 25–50 mg/kg IM or IV slowly or 1 Mark 1 kit (atropine + 2-PAM) if no other options exist	30 days–5 yrs	**Diazepam** 0.05–0.3 mg/kg IV to a max of 5 mg/dose OR **Lorazepam** 0.1 mg/kg slow IV (not to exceed 4 mg)
		Children (4–10 yrs)	**Atropine** 0.1 mg/kg IV/IM/IO or 3 doses of 1 mg AtroPen® (administer in rapid succession) and **2-PAM** 25–50 mg/kg IM or IV slowly OR 1 Mark 1 kit (atropine + 2-PAM) up to age 7, 2 Mark 1 kits for ages >7–10 yrs	5 yrs and older	**Diazepam** 0.05–0.3 mg/kg IV to a max of 10 mg/dose OR **Lorazepam** 0.1 mg/kg slow IV (not to exceed 4 mg)
		Adolescents (>10 yrs) and adults	**Atropine** 6 mg IM or 3 doses of 2 mg AtroPen® (administer in rapid succession) and **2-PAM** 1,800 mg IV/IM/IO OR 2 Mark 1 kits (atropine + 2-PAM) up to age 14, 3 Mark 1 kits for ages >14 yrs	Adolescents and adults	**Diazepam** 5–10 mg up to 30 mg in 8 h period OR **Lorazepam** 0.07 mg/kg slow IV (not to exceed 4 mg)

[a]In general, pralidoxime should be administered as soon as possible, no longer than 36 h after the termination of exposure. Pralidoxime can be diluted to 300 mg/ml for ease of IM administration. Maintenance infusion of 2-PAM at 10–20 mg/kg/h (max 2 g/h) has been described. Repeat atropine as needed every 5–10 min until pulmonary resistance improves, secretions resolve, or dyspnea decreases in a conscious patient. Hypoxia needs to be corrected as soon as possible.

glucose. None of the patients had hypocalcemia, renal dysfunction, or acidosis and all had complete recovery of pancreatic function. The authors concluded that acute pancreatitis, due to anticholinesterase intoxication, is not uncommon in the pediatric population (Weizman and Sofer, 1992). Pancreatitis has been described in adult exposures and the association has been investigated in animal studies (Weizman and Sofer, 1992).

EXHIBIT C (Pediatric Case Histories) – Carbamates/ Organophosphates

Carbamate Exposure in a Child

A 7-year-old female, previously healthy, was exposed to an unknown quantity of the fungicide pesticide maneb (manganese ethylene-bis-dithiocarbamate). She was admitted to the pediatric intensive care unit with status epilepticus. She had experienced abdominal pain with nausea, vomiting, and headache for approximately 3 days prior to admission. On the day of admission, she was pale, unconscious, staring, and hypotonic. Upon examination, it was determined that she also had severe hypothermia (32.5°C) and hypoventilation. In addition, she was found to have a combined metabolic and respiratory acidosis and elevated blood glucose levels. Routine diagnostic investigations such as blood counts, electrolytes, liver/renal function, CSF, and blood cultures, were normal. Urine/blood toxicology screens for barbiturates and benzodiazepines were negative. Liquid chromatographic-mass spectrometry confirmed the presence of maneb in her blood. Upon admission, the patient was intubated and her convulsions were treated with benzodiazepines. Within 24 h, there was a complete recovery of all neurological signs. Repeat physical and neurological exams were normal at 48 h. She was discharged 3 days after admission in good condition.

(*ref:* de Tollenaer *et al.*, 2006)

Case History: Organophosphate Exposure in a Child

A 2-year-old, previously healthy male ingested approximately 10 ml of the organophosphate insecticide demeton-*S*-methyl. Upon discovery of the ingestion, the child was disrobed and washed in the bathtub and then taken to the local hospital. Upon admission, which was approximately 30 min following the ingestion, the child was vomiting and salivating. Atropine was administered. He was then transferred to a larger hospital. During transport, he continued to have excessive salivation and experienced bradycardia. These episodes were treated with additional doses of atropine. Upon admission to the larger hospital, he was salivating, vomiting, and experiencing bronchial hypersecretion. At that time, his pupils were dilated with no reaction to light and he was tachycardic with a pulse rate of 150 bpm. At the hospital, gastic lavage was performed and additional doses of atropine administered. He was intubated prior to the completion of gastric lavage and given diazepam for sedation. Bradycardia (<100 bpm) stimulated the physicians to administer additional atropine. Due to the complexity of the case, the patient was transferred again to a hospital better equipped to handle his case. Upon that admission, the patient's blood pressure was 110/60 mm Hg, pulse 100 bpm, temperature 37.6°C, and his pupils were still dilated and unresponsive. Due to continued bronchial hypersecretion, additional atropine was administered. Obidoxime was administered twice, once at 9.5 and 11.5 h after the ingestion. After the oxime therapy, his condition stabilized and he was able to be extubated approximately 13 h after ingestion. Over the next 4 days, atropine was administered periodically to control mild bronchial hypersecretion. Electrolytes and chest X-rays were normal during the entire course of illness. A low hemoglobin and high alkaline phosphatase were the only abnormal labs. The patient was discharged 8 days after the ingestion in good condition. Plasma cholinesterase levels were initially decreased (<400 U/l), but they rose into the normal range by discharge. Twelve-month follow-up revealed that the child had no signs of neurological sequelae.

(*ref:* Rolfsjord *et al.*, 1998)

Another laboratory value that is often obtained in these exposures is serum pseudocholinesterase. Serum pseudocholinesterase activities are often assessed as normal in children because the reference standards may not be reliable when assessing children. To add to the complexity, the normal range of serum cholinesterase activity is wide (Sofer *et al.*, 1989). Authors have described the limitations of this measurement in determining therapy for children. In fact, it is recommended that a therapeutic and diagnostic trial of atropine should be given whenever there is any possibility of intoxication with these chemicals (Sofer *et al.*, 1989).

Additional laboratory abnormalities that have been reported in children are cardiac disturbances. Prolonged QTc intervals were reported in a few children exposed to organophosphates. However, there was spontaneous resolution with no evidence of ventricular dysrhythmia on electrocardiogram (Levy-Khademi *et al.*, 2007).

5. Pediatric Vulnerabilities

The clinical picture of anticholinesterase intoxication in children is very different to that of adults. Often, clinicians have difficulty in diagnosing the exposure in pediatric patients. In fact, in a retrospective review of OP/carbamate toxicity cases that were admitted to a Children's Medical Center in the USA, the transfer diagnosis was incorrect in 80% of the patients (Zwiener and Ginsburg, 1988). Patients were misdiagnosed with a wide variety of disease states that ranged from head trauma to cranial aneurysm to diabetic ketoacidosis. It was noted that the difficulty in identifying nicotinic and muscarinic signs in children may have contributed to the high misdiagnosis rate. For example, it may be difficult to distinguish normal infant crying from excessive lacrimation (Zwiener and Ginsburg, 1988).

The lack of classic muscarinic effects does not exclude the possibility of cholinesterase inhibitor poisoning in young children with central nervous system depression. In one case series, tearing and diaphoresis were not observed in pediatric patients (Lifshitz *et al.*, 1999). Miosis was absent in a number of pediatric patient cases reported in the literature with 27% of children in one case series lacking miosis on admission (Zwiener and Ginsburg, 1988). The percentage was 20% in another case series of pediatric patients (Sofer *et al.*, 1989).

Adult literature states that the most important signs of organophosphate toxicity are fasciculations and miosis. In one published pediatric case series, fasciculations were quite infrequent, occurring in only 16% of cases (Sofer *et al.*, 1989). Another pediatric case series verified this result, with the frequency of fasciculations being 22% (Zwiener and Ginsburg, 1988).

Another difference is the cardiac manifestations that are seen in adults compared to children. In one pediatric case series, cardiopulmonary manifestations were the least common, with tachyarrhythmias being more common than the bradyarrhythmias that are typically seen in adults (11 patients vs one patient) (Levy-Khademi *et al.*, 2007).

Compared to adults, neurological manifestations of toxicity were the most common in children. In one case series, significant hypotonia and muscle weakness were observed in all children (Lifshitz *et al.*, 1999). In addition, severe CNS depression with stupor and coma occurred in all the cases (Lifshitz *et al.*, 1999). In another case series, coma occurred in 54.8% and seizures in 38.7% of children who were accidentally exposed to organophosphates (Levy-Khademi *et al.*, 2007). It can be theorized that the more permeable blood–brain barrier in young children permits penetration of the toxic agents into the brain, thus causing CNS depression. Another theory is that in young children, cholinesterase inhibitors have a stronger affinity to acetylcholinesterase in the CNS and less affinity to cholinergic synapses in the autonomic ganglia (Lifshitz *et al.*, 1999). Accumulation of toxic compounds or their metabolites in the brain could also result in severe CNS dysfunction. Another thought is that the hypoxemia that has been observed in several pediatric cases could contribute to CNS depression (Sofer *et al.*, 1989).

6. Treatment

In all pediatric cases, supportive care was used to balance electrolyte disturbances and oxygen was administered for hypoxic episodes. Often, patients were intubated and given mechanical ventilation due to the excessive salivation and bronchial hypersecretion. Gastric lavage was utilized in one case of organophosphate ingestion (Rolfsjord *et al.*, 1998). The treatment of organophosphate intoxication mimics that of nerve agent exposures. Atropine and an oxime (such as pralidoxime) are the agents of choice for organophosphate exposures. Atropine therapy alone is recommended for carbamate exposure due to the fact that carbamates reversibly inhibit acetylcholinesterase, so there is little need for an agent such as an oxime, which reactivates the enzyme. In cholinesterase inhibitor poisoning, atropine will alleviate most of the muscarinic signs, few of the CNS symptoms, and almost none of the nicotinic symptoms (Lifshitz *et al.*, 1999).

Although atropine use is standard, clinicians are sometimes faced with the dilemma of administering atropine to a pediatric patient with an elevated heart rate. Due to the fact that children may manifest tachycardia with toxic exposures and the fact that the chronotropic effects of atropine may be minimal in infants and small children compared with healthy young adults, one group of authors suggests that atropine should not be withheld or administered in subtherapeutic doses in tachycardic infants and children with organophosphate or carbamate exposures. Their experience with pediatric patients showed that for patients with tachycardia at the time atropine was administered, their heart rate decreased and none of the patients developed cardiac arrhythmias (Zwiener and Ginsburg, 1988).

Use of oximes is well accepted for organophosphate exposures, but their role in carbamate poisoning is controversial. Animal studies have shown oxime use can increase toxicity when treating carbaryl exposures (Lifshitz *et al.*, 1994). Therefore, there is a general guideline that oximes should be avoided if a carbamate exposure is suspected. One case series reported the routine use of oxime therapy for carbamate exposures in children (Lifshitz *et al.*, 1994). Marked clinical improvement was observed in all patients regardless of whether they were exposed to an organophosphate or a carbamate. In addition to the retrospective review of cases, the authors completed an *in vitro* study of oxime use with carbamate toxicity and discovered that oximes play a minor role in direct reactivation of human carbamylated acetylcholinesterase. Due to this result, the authors concluded that the current guideline to avoid oxime use in a carbamate exposure is valid.

Fortunately, in most cases of organophosphate or carbamate toxicity, pediatric patients had a full recovery if they were diagnosed rapidly and appropriate treatments were administered in a timely fashion.

7. Summary

There is a limited amount of literature available describing the toxicities of organophosphate and carbamate exposures in pediatrics. What literature is available describes major differences between the manners children manifest toxicity compared to adults. It is critical to understand these differences so that patients are not misdiagnosed and appropriate therapy is not delayed. In general, the CNS toxicities are greater in children than in adults with coma, stupor, and seizures being common. It is important to recognize that if therapy is given in a timely manner, complete recovery is often the outcome for children exposed to these toxic agents.

C. Vesicants

1. Introduction

Blister agents or vesicants are chemicals that cause blister or vesicle formation upon dermal contact. Agents such as mustards or lewisite have been used as chemical warfare agents in the past (Yu *et al.*, 2003). Although these agents have less toxicity than nerve agents, they cause prolonged morbidity. There are two types of mustard, termed sulfur mustard (HD) and nitrogen mustards (HNs). HD caused

EXHIBIT D (Pediatric Case Histories) – Vesicants

Mustard Gas Exposure in 14 Children/Teenagers from Halabja, Iraq

Mustard gas was used on the civilian population during the Iraq-Iran War (1980–88). A case series of 14 children and teenagers affected by mustard gas was reported by Momeni *et al.* They found that facial involvement was the most frequent disorder (78%), followed by genital (42%), trunkal and axillar lesions (both 14%). The most prominent laboratory abnormality was eosinophilia (12% of patients). As far as the time course of toxicity, skin lesions appeared 4–18 h after exposure and then erythema developed within 20–30 h. After the erythema, blisters would appear. The authors concluded that the time of onset of toxicity was shorter and more severe in children and teenagers compared with adults.

(*ref*: Momeni and Aminjavaheri, 1994)

Clinical Cases from Mofid Medical Center (Mustard Exposure Following the Halabja Attack on March 17, 1988)

A 3-year-old (yo) male presented to Mofid Medical Center 8 days after the Halabja chemical attack with fever (39.5°C), tachycardia (HR 140), and tachypnea (RR 60). Cutaneous skin lesions were mild, but erythema and edema covered 45 % of his skin surface area. Ocular and respiratory findings were as previously described. Laboratory findings were unremarkable except for a mild anemia. Chest roentograms revealed hilar congestion and consolidation bilaterally. The fever continued despite antibiotic therapy. On day 10 of admission (18 days after exposure), the patient developed leukocytosis with 82% PMNs and worsening respiratory distress. The patient finally died 21 days after exposure.

An 8-yo Iranian male presented at 5:30 pm with fever (40°C), severe agitation, delirium and somnolence 24 h after exposure to chemical agents the previous day in Halabja. BP was 110/70 mm Hg and the patient was notably tachycardic (HR 120), and tachypneic (RR 42). The patient was noted to have serious dermatologic, ocular, and respiratory impairment. Erythema, vesicles, erosions, bullae, ulcerations, and edema was present on 35% of the body. Ocular manifestations included conjunctivitis and palpebral edema. At this point, the patient was working hard to breathe as evidenced from accessory muscles of respiration (sternocleidomastoid). On physical examination of the lungs, wheezing and crepitation were noted throughout all lung field. Laboratory findings were the following: Na^+ 139, K^+ 4.1 mEq/l, BUN 25 mg/dl, calcium 7.3 mg/dl, and WBC 9,900/mm^3 with 90% neutrophils. Arterial blood gases: pH 7.30, pCO_2 31, pO_2 65, and HCO_3 15.1. Chest roentograms showed bilateral infiltrates. The patient died 24 h after admission and 48 h after exposure, despite receiving supportive care.

(*ref:* Azizi and Amid, 1990)

more casualties in WWI than any other chemical weapon. It caused a significant number of casualties, both civilian and military, during the Iran–Iraq War of the 1980s. HD vapor is the route most likely to be used by terror groups (Yu *et al.*, 2003). It affects multiple organ systems including skin, eyes, respiratory and gastrointestinal tracts, and bone marrow (Yu *et al.*, 2003). Nitrogen mustards, on the other hand, have never been used on the battlefield and will not be discussed further.

Lewisite, a vesicant with HD-like properties, causes a similar constellation of signs and symptoms involving the skin, eyes, and airways as well as systemic effects (e.g. increased capillary permeability) after absorption. However, it does not produce immunological suppression like mustard. Another difference is that the management of lewisite toxicity includes an antidote, British Anti-Lewisite (BAL) (Yu *et al.*, 2003).

2. Mechanism of Toxicity

HD rapidly penetrates cells and generates a highly toxic reaction that disrupts cell function and eventually causes cell death (Sidell *et al.*, 1997). It is classified as an alkylating agent, targeting poorly differentiated and rapidly reproducing cells (Yu *et al.*, 2003). Death is a result of massive pulmonary damage complicated by infection.

3. Clinical Presentation

Mustard can cause local effects on skin, airways, and eyes; however, large doses can cause fatal systemic effects (Yu *et al.*, 2003). In a study of clinical findings among children exposed to vesicants, ocular, cutaneous, and respiratory signs were the most prevalent (Azizi and Amid, 1990). Ocular findings consisted of the following: conjunctivitis (94%), palpebral edema (81%), eye closure (63%), keratitis (38%), blepharospasm (25%), corneal ulceration (19%), and chemosis (6%). Cutaneous signs included erythema (94%), hyperpigmentation (75%), ulceration (69%), erosion (63%), blister (56%), edema (50%), vesicles (31%), and hypopigmentation (13%). Respiratory signs included dyspnea (63%), crepitation (50%), and wheezing (25%).

Other pediatric signs of mustard exposure were photophobia, lacrimation, ophthalmalgia, and eye burning (94%). Dry cough (81%), dermal pain, and burning (94%) were also frequent complaints. Less frequent complaints were diplopia, itchy eyes, sore throat, sneezing, nasal secretions, dyspnea, burning sensation of the upper respiratory tract, suffocation, and dysphonia (Azizi and Amid, 1990).

Initial dermal signs of toxicity consist of erythema, occurring 4–8 h after exposure. Pruritus can occur with or prior to erythema (Yu *et al.*, 2003; Azizi and Amid, 1990). Over the next 24 h, large yellowish blisters form in areas of

thin skin such as the groin and underarms. Eye damage can occur, ranging in spectrum from pain and irritation to blindness. Mustard also causes clinical effects that can be delayed for hours (Yu *et al.*, 2003; Sidell *et al.*, 1997; Azizi and Amid, 1990). This causes victims not to recognize toxicity until well after exposure. During this time lag, sulfur works to subclinically damage the skin. This latent period is significant because the shorter the latent period, the more severe the exposure, and the worse the outcome.

The CNS and bone marrow can also be affected, as displayed by symptoms of fatigue, headaches, and depression (Sidell *et al.*, 1997). HD can also lead to pneumonia, the cause of death for many HD casualties in WWI due to lack of antibiotics. A leukopenic pneumonia usually occurs between 6 and 10 days after HD exposure. The manifestation of leukopenia (specifically lymphopenia) results from the myelosuppressive effects of mustard agents.

4. Laboratory findings

While there is no diagnostic confirmatory test for mustard exposure, some laboratory tests can prove useful. As described above, inflammation and infection will show up as fever and leukocytosis. Erythrocyte sedimentation rate (ESR) has been shown to be elevated in patients after mustard exposure (Motakallem, 1988). Some of these patients were in the pediatric age range of 0–18 years. CBC determinations may show abnormalities depending on the severity of the vapor inhalation or exposure (Yu *et al.*, 2003; Azizi and Amid, 1990). The CBC may show a low hematocrit and leukopenia if the exposure was severe. There may be only a transient decrease in WBC with subsequent recovery. In pediatric cases of HD vapor exposure, decreases in hematocrit and/or WBC were likely to occur in the first 2 weeks, with the lowest levels of Hb, Hct, WBC, and neutrophil count observed in the 6th to 10th day samples after exposure (Azizi and Amid, 1990).

These pediatric patients also suffered from clear signs of hypoxemia and renal failure (Azizi and Amid, 1990). Unfortunately, serum creatinine and renal function tests (RFTs) were not found in the charts. Arterial blood gases (ABGs) may provide useful information, but they may show a varied picture. In one pediatric study of mustard casualties, most (43%) cases showed a simple metabolic acidosis. The other groups showed showed the following:

- mixed metabolic acidosis and respiratory alkalosis (29%)
- simple respiratory alkalosis (14%)
- mixed metabolic and respiratory acidosis (7%)
- mixed metabolic alkalosis and respiratory acidosis (7%).

Blood urea nitrogen can be elevated with mustard exposure, but it does not necessarily predict outcome or mortality. Blood urea nitrogen was significantly elevated in severe mustard exposure cases in the Azizi study; three of the four pediatric mustard victims that died showed very high blood urea nitrogen (Azizi and Amid, 1990). While elevations in blood urea nitrogen were found in many of the pediatric casualties from mustard exposure, blood urea nitrogen returned to normal levels soon afterwards in survivors.

5. Pediatric Vulnerability

The effects of sulfur mustard on children are more severe than on adults (Yu *et al.*, 2003). Premature infants have thinner skin, and the dermal–epidermal junction is not fully developed in children (Rutter and Hull, 1979; Harpin and Rutter, 1983; Nopper *et al.*, 1996; Seidenari *et al.*, 2000; Mancini, 2004); therefore, the time between exposure and onset of blisters is shortened, and the number and severity of blisters will be more severe (Yu *et al.*, 2003). In fact, lesions in children exposed to mustard have been shown to be more severe. Initial index cases of mass casualties are typically children. Eye findings tend to be greater in children because of their inability to protect themselves and tendency to rub their eyes (Yu *et al.*, 2003; Azizi and Amid, 1990). Children are also shown to be more susceptible to pulmonary injury for reasons previously discussed. One case report looked at the long-term effects of mustard exposure in a child (Dompeling *et al.*, 2004). Acutely, the child suffered a severe chemical pneumonia; the long-term consequence was chronic bronchiolitis. Finally, signs of gastrointestinal toxicity may be greater in children secondary to fluid losses in combination with lower intravascular volume reserves (Yu *et al.*, 2003).

While the decision to evacuate and hospitalize HD casualties is based on the extent [total body surface area (TBSA) > 5%], severity of the skin lesions, and the recognition of multiple organ involvement (Graham *et al.*, 2005), the threshold to hospitalize children with HD injuries should be lower. One reason is that vapor mustard used by terrorists may cause extensive pulmonary involvement while producing mild skin blisters.

6. Treatment

While decontamination and supportive therapy are the mainstays of treatment, antidotes to counteract HD vapor, aerosol, or liquid exposures do not exist (Yu *et al.*, 2003). Adult decontamination may include bleach solutions; however, this method can cause greater toxicity in children. Soap and water are the preferred agents to use for decontamination in children. Supportive care consists of the management of pulmonary and skin manifestations such as the use of cough suppressants and/or topical silver sulfadiazine for burns (Yu *et al.*, 2003; Sidell *et al.*, 1997; Azizi and Amid, 1990). Pediatric dosage and treatment recommendations for vesicant exposures are displayed in Table 61.5.

There are currently no standardized guidelines of casualty management or drugs available to prevent HD effects on skin and mucous membranes (Sidell *et al.*, 1997; Graham *et al.*,

TABLE 61.5. Management of vesicant exposures (Momeni and Aminjavaheri, 1994; Yu *et al.*, 2003)

Vesicant agents	Symptoms	Antidotes/treatment
Mustard	• Skin erythema and pruritis • Development of large yellow blisters leading to ulcers • Eye damage • Inhalational damage: hoarseness and cough, mucosal necrosis, toneless voice, nausea, vomiting	**Decontamination:** soap, water, no bleach Copious water irrigation for eyes **Pulmonary management:** cough suppressants, throat lozenges **Skin management:** topical agents used for burns (1% silver sulfadiazine), antibiotics for secondary infections (Neosporin®), antihistamines for itching (diphenhydramine 1 mg/kg/dose orally q6–8 h max 300 mg/day, hydroxyzine 0.5 mg/kg/dose orally q6–8 h) **Immune system management:** G-CSF (filgrastim) 5–10 micrograms/kg/day subcutaneous for neutropenia
Lewisite	• Shock • Pulmonary injury • Blisters	**Decontamination:** soap, water, no bleach **Antidote:** BAL-dimercaprol may decrease systemic effects of lewisite **Pulmonary management:** BAL 3–5 mg/kg deep IM q4 h × 4 doses (dose depends on severity of exposure and symptoms) **Skin management:** BAL ointment **Eye management:** BAL ophthalmic ointment

2005). The mainstay of treatment is prompt decontamination, blister aspiration or deroofing (epidermal removal), physical debridement, irrigation, topical antibiotics, and sterile dressing application for cutaneous HD injuries. Current treatment strategies rely on symptomatic management to relieve symptoms, prevent infections, and promote healing. The general recommendations are described in the *Medical Management of Chemical Casualties Handbook* (USAMRICD, 2000a), the Field Management of Chemical Casualties Handbook (USAMRICD, 2000b), and other references (Graham *et al.*, 2005). We will discuss the aspects of treatment that relate to the pediatric population. Most pediatric casualties will have involvement of multiple organ systems (skin, ocular, gastrointestinal, bone marrow, respiratory, etc.) as documented by Iranian physicians treating pediatric casualties of HD vapor during the Iran–Iraq War (Azizi and Amid, 1990).

a. Dermatological Management

Managing mustard skin lesions is especially challenging in the pediatric population. The goal of blister management is to keep the patient comfortable, keep the lesions clean, and prevent infection. Children especially will be extremely anxious at the sight of bullae and erythema in addition to the burning, pruritis, and allodynia associated with HD blisters (Sidell *et al.*, 1997). Anxiolytics may be appropriate to calm them down and prevent them from picking at bullae. Burning and itching associated with erythema can be relieved by calamine or soothing lotion/cream such as 0.25% camphor, menthol corticosteroids, antipruritics (i.e. diphenhydramine), and silver sulfadiazine cream (Sidell *et al.*, 1997; Azizi and Amid, 1990). Pain and discomfort can be relieved with systemic analgesics. Systemic analgesics such as morphine should be given liberally before manipulation of the burned area.

Vapor mustard typically causes a first- or second-degree burn, while liquid mustard produces damage similar to a third-degree burn. In either case, tense bullae are the hallmark of HD injuries. Bullae are typically dome shaped, thin walled, 0.5 to 5.0 cm in diameter, superficial, translucent, yellowish, multiloculated, honeycombed (Moradi *et al.*, 1986), and surrounded by erythema (Sidell *et al.*, 1997). Preventing children from breaking the blisters can be a challenge, especially when constant friction from clothing and blankets is irritating to the skin. These areas should be wrapped in protective dressings. Graham *et al.* (2005) have made an important point about the existence of a reservoir of unbound HD in human skin following a vapor (Logan *et al.*, 2000) or liquid exposure, leading to an off-gassing period. They suggested that this off-gassing period can last for 24 to 36 h, whereby application of an occlusive dressing is not beneficial to prevent vapor build-up (Graham *et al.*, 2005).

It is recommended that small blisters (<1 cm) should be left alone on the child, but the immediately surrounding area should be cleaned, irrigated daily, and covered with topical antibiotic (Sidell *et al.*, 1997). Petroleum gauze bandage dressings should be wrapped around these unbroken blisters and changed every few days. Larger blisters (>1 cm) should be unroofed and irrigated several times a day with saline, sterile water, clean soapy water, or Dakin's solution and covered with topical antibiotic cream or ointment. It should be noted that blister fluid does not contain mustard (Buscher and Conway, 1944) and therefore does not represent a hazard to the health care worker. Options for topical

antibiotic creams in children include silver sulfadiazine, and triple combination antibiotic (bacitracin, neomycin sulfate, and polymyxin B sulfate) (Sidell *et al.*, 1997) but not mafenide acetate, which can cause toxicities in children (Geffner *et al.*, 1981; Ohlgisser *et al.*, 1978). These topical antibiotics should be applied to the area of bullae and surrounding areas of erythema. There is no information comparing use of this combination (triple antibiotic topical ointment) in children with use in other age groups.

While skin healing can take months for completion, pigment changes (hyper- or hypopigmentation) can persist (Sidell *et al.*, 1997; Graham *et al.*, 2005). It is also important to note that not all burn injuries require treatment at a burn center. Patients will require aggressive pain management and close observation for the systemic effects of HD exposure. Skin grafting, although rare, has been successfully used for deep burns (Ruhl *et al.*, 1994).

b. Ophthalmology

The objective for any ophthalmology consultation on pediatric HD injuries involving the eye is prevention of scarring and infection (Sidell *et al.*, 1997). Eyes exposed to HD should be irrigated to remove traces of vesicant. Severe ocular involvement requires topical antibiotics (tobramycin OD) applied several times a day. Topical steroids may be useful in the first 48 h after exposure. Temporary loss of vision may also occur after mustard exposure (Sidell *et al.*, 1997; Azizi and Amid, 1990; Motakallem, 1988). The patient should be reassured that vision loss is not permanent and is due to palpebral edema and not corneal damage.

c. Respiratory System

The conducting and ventilation portions of the respiratory tract are affected with HD vapor, necessitating a pulmonary examination (Dompeling *et al.*, 2004; Sidell *et al.*, 1997; Azizi and Amid, 1990). Bronchodilators are useful to diminish hyperreactive airways and should be used if a prior history of asthma or hyperreactive airways is documented. Further support with humidified oxygen may be required. Ventilatory support may be required for severe cases of HD vapor exposure before laryngeal spasm makes intubation difficult. Bronchoscopy is critical for diagnosis, therapeutic dilation against HD-induced tracheobronchial stenosis, and removal of pseudomembranes that cause airway obstruction.

Since the toxic bronchitis produced by HD is nonbacterial, antibiotic therapy should not be given during the first 3 to 4 days (Sidell *et al.*,1997). Continuous monitoring of sputum for Gram's stain and culture growth is necessary to identify the specific organism responsible for the late developing superinfection. The presence of leukopenia in children, a grave sign of HD exposure, will necessitate aggressive support with combination antibiotic treatment.

d. Gastrointestinal Tract

Atropine or common antiemetics can be given to provide relief from nausea and vomiting, early signs of HD intoxication (Yu *et al.*, 2003). Excellent choices for pediatric-specific antiemetics include medications such as promethazine, metoclopramide and ondansetron (Sidell *et al.*, 1997). Persistent vomiting and diarrhea are a later sign of systemic toxicity and require prompt fluid replacement.

e. Bone Marrow Suppression

As a radiomimetic, HD affects rapidly dividing tissues like bone marrow in addition to the gastrointestinal tract (Sidell *et al.*, 1997; Graham *et al.*, 2005). HD destroys hematopoietic precursor cells; WBCs have the shortest life span and decrease in number first, followed by RBCs and thrombocytes. The bone marrow suppression that is sometimes seen can be treated with filgrastim injections. This medication stimulates the bone marrow to create and release white blood cells.

f. Other Treatment Considerations

Fluid status, electrolytes, and urine output should be monitored in the HD-intoxicated patient. Tetanus prophylaxis should also be administered because fatal tetanus may occur even after a small partial-thickness burn (Marshall *et al.*, 1972).

7. Summary

Pediatric exposures to vesicants can be quite toxic; however, in contrast to nerve agent exposures, HD causes significantly greater morbidity than mortality. While mustard did not cause many deaths in WWI, death from HD exposure is usually due to massive pulmonary damage complicated by infection (bronchopneumonia) and sepsis. Children often show a quicker onset and greater severity of toxicity. Skin and eye toxicity occurs in the form of blisters or irritation that can result in blindness for the most severe cases. Except for lewisite, vesicant exposures must be managed with supportive care and rapid decontamination.

D. Pulmonary Agents

1. Introduction

In January 2002, a Central Intelligence Agency (CIA) report stated that terrorist groups may have less interest in biological materials compared to chemicals such as cyanide, chlorine, and phosgene (DCI, 2002) which are able to contaminate food and water supplies (Sidell *et al.*, 1997; Graham *et al.*, 2005). The targeting of children has the potential to destabilize governments and create widespread terror. Industrial chemicals, such as chlorine and phosgene, have advantages that make them potential candidates to be used by terrorists in the future. Both chlorine and phosgene are fairly easy to manufacture and handle, prompting national concern over their future use. In the USA alone, millions of tons of chlorine and phosgene are produced annually toward the manufacture of various products (Burklow *et al.*, 2003). A detailed discussion of the general mechanisms of chlorine and phosgene toxicity can be found

EXHIBIT E (Pediatric Case History) – Pulmonary Agents

Chlorine Gas Exposure in an Adolescent

A 14-year-old male, previously healthy except for a history of asthma, was exposed to chlorine gas when he mixed household bleach with vinegar. Immediately, he began to cough and have difficulty breathing. His symptoms worsened over the next hour, leading to an admission to the local emergency room. Upon admission, the physical exam revealed that the patient was in respiratory distress with bilateral crackles and diffuse wheezing. He also had conjunctival irritation. Vital signs were pulse 100 bpm, blood pressure of 130/80 mm Hg, respiratory rate of 20/min and a temperature of 97°F. His initial oxygen saturation while breathing room air was 92%. A venous blood gas suggested mild CO_2 retention with a pH of 7.35, PCO_2 of 53 mm Hg, and a PO_2 of 33 mm Hg. Chest radiograph showed bilateral alveolar infiltrates with a normal heart size, which is indicative of acute lung injury. Sinus tachycardia was demonstrated on the electrocardiogram. The patient was treated with oxygen, multiple doses of nebulized albuterol and oral prednisone. Despite these measures, his overall respiratory status continued to decline and a repeat pulse oximetry while on 50% oxygen showed a saturation of 85%. Due to his worsening course, he was intubated and transported to another hospital with a pediatric intensive care unit. Upon intubation, it was noted that the patient had copious secretions. After admission to the PICU, the patient developed acute respiratory distress syndromes (ARDS) and needed ventilatory management for 19 days along with additional doses of albuterol and methylprednisolone. After extubation, he was placed on a prednisone taper and discharged with no evidence of residual pulmonary dysfunction.

(*ref:* Traub *et al.*, 2002)

elsewhere in this textbook and will not be explored further here.

2. Clinical Presentation

Pediatric signs and symptoms of chlorine gas exposure include predominantly ocular, nasal, oropharyngeal, and pulmonary irritation of membranes (Burklow *et al.*, 2003). The hallmark of intoxication by these choking agents involves respiratory complaints. Minor chlorine exposures can lead to burning of the eyes and throat, indicative of mucous membrane irritation. More severely exposed patients may complain of cough, choking, sore throat, shortness of breath, chest tightness, difficulty breathing, and other respiratory-related complaints. Clinical findings may also include lacrimation, rhinorrhea, laryngeal edema, hoarseness, aphonia, stridor, expiratory wheezing, tracheitis, and cyanosis (Güloğlu *et al.*, 2002; Traub *et al.*, 2002). Tachypnea may develop as a direct result of pulmonary irritation, and tachycardia has been demonstrated in some studies. Many pediatric patients with a prior history of reactive airway disease are at increased risk of chlorine-induced bronchospasm (Burklow *et al.*, 2003).

Pulse oximetry may indicate low oxygen saturation (Traub *et al.*, 2002). While arterial blood gases usually indicate hypoxemia, carbon dioxide levels have been shown to be decreased, increased, or normal (Güloğlu *et al.*, 2002; Traub *et al.*, 2002). A hyperchloremic metabolic acidosis may show up on blood chemistries due to systemic absorption of hydrochloric acid.

Pulmonary edema, the most significant morbidity from pulmonary agents, can be seen on chest roentograms (Burklow *et al.*, 2003). Pulmonary edema may develop as early as 2 to 4 h after exposure; radiographic evidence typically appears later. Pulmonary edema may progress to the point of producing Kerley B lines on chest x-rays. These lines are often described as rungs of a ladder running perpendicular to the lateral margin of the lungs, beginning at the costophrenic angle. Chest radiographs will often show opacities of acute lung injury. Pneumomediastinum has also been reported in chlorine gas exposure (Traub *et al.*, 2002).

Pulmonary function tests (PFTs) are not helpful (Traub *et al.*, 2002; Pherwani *et al.*, 1989). A study of school children exposed to a chlorine gas leak reported a predominantly obstructive pattern on PFTs. This could be explained by congestion and edema narrowing the central airways rather than smaller airways.

3. Pediatric Vulnerability

Chlorine is a pungent green–yellow gas, twice as heavy as air (Güloğlu *et al.*, 2002) and settles near the ground (Burklow *et al.*, 2003; Traub *et al.*, 2002). This poses a problem for children, leading to increased exposure for this population in the event of accidental release or an act of terror. Children can be exposed as a result of the following activities: inhaling chlorine vapors at swimming pools (Burklow *et al.*, 2003), mixing of household bleach (sodium hypochlorite) with acidic cleaning agents (Traub *et al.*, 2002), and industrial accidents (Pherwani *et al.*, 1989). Phosgene, a dense gas heavier than air, is a more lethal pulmonary agent than chlorine. While the smell of chlorine is associated with swimming pools, phosgene odor is described as freshly mown hay (Burklow *et al.*, 2003).

Initially, both agents cause intense irritation of the mucosal membranes (Burklow *et al.*, 2003) and coughing (Güloğlu *et al.*, 2002; Traub *et al.*, 2002). This is typically followed by a feeling of suffocation (Burklow *et al.*, 2003). Morbidity from pulmonary agents is the direct result of pulmonary edema, appearing 2–4 h after chlorine exposures. Since children have a smaller fluid reserve (Rotenberg and Newmark, 2003), pulmonary edema can cause rapid dehydration or even shock (Burklow *et al.*, 2003). Due to the higher respiratory rates and minute

TABLE 61.6. Management of pulmonary agent exposures (Burklow *et al.*, 2003)

Pulmonary agents	Symptoms	Treatment
Chlorine	• Lacrimation • Rhinorrhea • Conjunctival irritation • Cough • Sore throat • Hoarseness • Laryngeal edema • Dyspnea • Stridor • ARDS • Pulmonary edema	**Decontamination:** Copious water irrigation of the skin, eyes, and mucosal membranes to prevent continued irritation and injury **Symptomatic care (no antidote):** Warm/moist air, supplemental oxygen, positive pressure O_2 for pulmonary edema **Bronchospasm:** Beta-agonists (albuterol) **Severe bronchospasm:** Corticosteroids (prednisone) (also used for PTS with H/O asthma but use unproven) **Analgesia and cough:** Nebulized lidocaine (4% topical solution) or nebulized sodium bicarbonate (use unproven)
Phosgene	• Transient irritation (eyes, nose, throat, and sinus) • Bronchospasm • Pulmonary edema • Apnea • Hypoxia	**Decontamination:** Wash away all residual liquid with copious water, remove clothing **Symptomatic care:** ABCs, hydrate, positive pressure O_2 for pulmonary edema **Bronchospasm:** Beta-agonists (albuterol), corticosteroids INH/IV, furosemide contraindicated **Hypoxia:** Oxygen

volumes of children (Rotenberg and Newmark, 2003), exposure to pulmonary agents will be greater (Burklow *et al.*, 2003). Concerning the effects on children exposed to pulmonary agents and subsequent treatment, there are many documented clinical case studies in the literature as a result of accidental exposures and industrial accidents (Güloğlu *et al.*, 2002; Traub *et al.*, 2002; Pherwani *et al.*, 1989).

4. Treatment

The first line of treatment for children exposed to pulmonary agents is decontamination. Decontamination can be as simple as removing the victim from the source to fresh air, followed by the removal of contaminated clothing (Burklow *et al.*, 2003). Supportive care includes administration of humidified air, supplemental oxygen, water irrigation, and high flow oxygen delivered via positive pressure for pulmonary edema (Burklow *et al.*, 2003; Traub *et al.*, 2002). Further treatment may include surgical debridement, supportive care with medications such as albuterol for bronchospasm, corticosteroids for inflammation, and antibiotics for any secondary bacterial infections. Antidotes or specific post-exposure treatments do not exist for this class of agents. Supportive treatment recommendations are shown in Table 61.6.

5. Summary

Chlorine and phosgene are two chemicals that can cause severe pulmonary toxicity due to pulmonary edema and direct damage to the lungs. Treatment involves decontamination and supportive care. Special care needs to be provided for exposed children because they are at higher risk for toxicity because of their unique vulnerabilities.

E. Cyanide

1. Introduction

Cyanide is used in plastic processing, electroplating of metals, metal tempering, extraction of gold and silver, fumigants, and photographic development (Rotenberg, 2003a; Baskin and Brewer, 1997). It is also found in vehicle exhaust, tobacco smoke, certain fruit pits and bitter almonds. The major cyanide containing compounds used by the military in WWI were hydrogen cyanide, cyanogen chloride, and cyanogen bromide. Cyanide is also liberated during the combustion or metabolism of nitrogen containing polymers of natural and synthetic origin (Riordan *et al.*, 2002). Cyanides can cause lethality through inhalation of cyanide vapor or ingestion (Prajapati *et al.*, 1992). Cyanide poisoning leads to death in minutes but can be effectively treated with antidotes if diagnosed early. Pediatricians, medical first responders, and firefighters need to recognize victims of cyanide poisoning in order to initiate immediate intervention (Rotenberg, 2003a; Baskin and Brewer, 1997). Cyanide is one of the few chemicals for which an effective antidote exists.

2. Mechanism of Toxicity

The cyanide ion kills aerobic organisms by shutting down oxidative phosphorylation in the mitrochondria and therefore the utilization of oxygen in cells (Baskin and Brewer, 1997; Riordan *et al.*, 2002). Cyanide has a propensity to affect certain organs (e.g. brain, heart, and lungs) more than

EXHIBIT F (Pediatric Case History) – Cyanide

Case History: Cyanide Exposure in a Child

A 2-year-old, previously healthy, 12 kg male ingested an unknown quantity of an acetonitrile-containing sculptured nail remover. The product contains an aliphatic nitrile that releases inorganic cyanide upon human metabolization. The child was brought into the emergency room because of lethargy approximately 10 h after the ingestion. Although the child was acting normally at the time of ingestion, 8 h later, he was found to be moaning, poorly responsive, and having just vomited. In the emergency room, he was pale and lethargic, responding only to deep pain. Abdomen and neck exam was normal and the lung exam revealed bilateral coarse breath sounds with a normal chest roentgenogram. Extremities were mottled and cool with a delayed capillary refill time. Vital signs showed a temperature of 36.9°C, pulse of 140 bpm, respiratory rate of 56/min, and blood pressure of 70/30 mm Hg. Arterial blood gas measurements showed a pH of 6.95, PCO_2 of 11 mm Hg, and PO_2 of 114 mm Hg. His electrolytes revealed a sodium of 137 mmol/l, potassium of 5.1 mmol/l, chloride of 114 mmol/l, bicarbonate of 4 mmol/l, serum creatinine of 70.7 μmol/l, glucose of 15.8 mmol/l, and a blood urea nitrogen of 5 mmol/l. The white blood cell count was 9.5×10^9/l and the hematocrit was 31%. Sinus tachycardia, at a rate of 160 bpm, with normal intervals and axis, was observed on the electrocardiogram. Serial whole-blood cyanide levels were obtained with the initial level being 231 μmol/l (600 μg/dl) 12 h after the exposure. The patient was given oxygen, sodium bicarbonate, and fluid resuscitation. Electrolyte and acid–base disturbances were corrected and no antidotal therapy was administered due to prompt response on supportive therapies. The patient was discharged from the hospital 3 days after admission in good condition.

(*ref:* Caravati and Litovitz, 1988)

others (Rotenberg, 2003a; Baskin and Brewer, 1997). Significant exposure can lead to central respiratory arrest and myocardial depression. Cyanide also acts as a direct neurotoxin (Rotenberg, 2003a), disrupting cell membranes and causing excitatory injury in the central nervous system (CNS) (Baskin and Brewer, 1997; Riordan *et al.*, 2002).

3. Clinical Presentation

Cyanide is an uncommon cause of childhood poisoning. In 2006, there were only 12 reported cases of cyanide exposure in the pediatric population (<19 years) (Bronstein *et al.*, 2007). Since signs of toxicity (see Exhibit F) are so similar to carbon monoxide poisoning, which accounts for the largest group of poisoning deaths among children, clinicians must have a high index of suspicion to make the diagnosis (Riordan *et al.*, 2002; Prajapati *et al.*, 1992). Rotenberg describes a typical toxidrome induced by cyanide (Rotenberg, 2003a). This includes a rapid progression from hyperpnea, anxiety, restlessness, unconsciousness, seizures, apnea, and finally death. Skin, blood, and fundi may be cherry red upon physical examination due to the inability of mitochondria to extract oxygen. In reported cases of accidental cyanide ingestion by children, other signs of toxicity included nausea, vomiting, abdominal pain, headache, lethargy, slurred speech, ataxia, stupor, coma, and respiratory depression. In addition, delayed vomiting occurred due to the slow metabolization of the chemical compound acetonitrile to cyanide, a process that can take 6 to 14 h after the ingestion (Geller *et al.*, 2006).

4. Laboratory Findings

Arterial blood gases can provide clues for cyanide exposure. Classic cases are presented with severe metabolic acidosis, elevated anion gap and high lactate concentrations (Rotenberg, 2003a). Impaired cellular respiration will lead to a high oxygen content in venous blood (Rotenberg, 2003a; Riordan *et al.*, 2002). Thus, a reduced arterial-venous oxygen saturation difference suggests this diagnosis. Blood cyanide levels are confirmatory (Rotenberg, 2003a; Baskin and Brewer, 1997; Riordan *et al.*, 2002) but will only delay the diagnosis, which must be based on the initial clinical presentation. Immediate therapeutic intervention with provision of 100% supplemental oxygen and administration of specific antidotes is paramount. An

EXHIBIT G

Mnemonic for Recognition of Cyanide Toxicity

F-A-T R-E-D C-A-T-S

Flushing of skin
Almonds (bitter almond smell)
Tachycardia

Red (Red/pink skin, bright red retinal vessels)
Excitation of nervous system
Dizziness, **D**eath, recent **D**epression history

Confusion, **C**oma, **C**onvulsions
Acidosis (metabolic or lactic), **A**nion gap
Tachypnea
Soot in nose

almond-like odor on the breath may alert a clinician that a person may have been exposed to cyanide, but up to 40% of the general population is unable to detect this odor.

5. Pediatric Vulnerability

Children are especially vulnerable to cyanide attacks (Rotenberg, 2003a). A larger exposure to cyanide vapor occurs due to the higher respiratory rates and higher surface-to-volume ratios in children. Cyanide liquid causes greater and more rapid absorption when it comes against the immature skin barrier of children. Lower body mass and immature metabolic processes can render children more susceptible than adults to toxicity from cyanide exposure. It has also been noted that children seem more susceptible to ingestion poisoning as demonstrated by various cassava and apricot pit exposures where the severity of toxicity was greater than that seen in adults who were also ingesting these products. In fact, it has been theorized that due to children's higher gastric acidity, leading to greater absorption, they experience more severe toxicity than adults when cassava is ingested (Geller *et al.*, 2006). A case report of potassium cyanide ingestion among ten children reported that the initial symptoms seen included abdominal pain, nausea, restlessness, and giddiness (Prajapati *et al.*, 1992). Cyanosis and drowsiness were also noted, but the signature cherry red skin color was not reported. Post mortem examination from the two children that died showed bright red blood and tissues with congestion. These two children consumed powder packets of potassium cyanide mixed in water, while the other eight children licked the powder, leading to less toxicity. The survivors were managed with aggressive supportive care including gastric lavage, oxygen, and intravenous fluids.

6. Treatment

The mainstay of treatment in cases of cyanide toxicity in the USA consists of supportive treatment and use of a multi-stage antidote kit (Rotenberg, 2003a; Baskin and Brewer, 1997; Riordan *et al.*, 2002). Table 61.7 details pediatric doses used for the medications in this kit, which contains amyl nitrite, sodium nitrite, and sodium thiosulfate. Antidotes should be provided only for significantly symptomatic patients, such as those with impaired consciousness, seizures, acidosis, hypotension, hyperkalemia, or unstable vital signs (Goldfrank *et al.*, 1998). Even when patients are rendered comatose by the inhalation of hydrogen cyanide gas, antidotes may not be necessary if the exposure is rapidly terminated, the patient has regained consciousness on arrival to the hospital, and there is no acidosis or abnormality of the vital signs (Peden *et al.*, 1986).

7. Supportive Therapy

Irrespective of the antidote treatment available, treatment will always consist of supportive therapy (Rotenberg, 2003a). Supportive therapy alone may reverse the effects of cyanide even in the face of apnea (Rotenberg, 2003a; Baskin and Brewer, 1997; Peden *et al.*, 1986). Supportive therapy includes decontamination, which includes gastric lavage and/or administration of activated charcoal if appropriate, oxygen, hydration, and anticonvulsants. Decontamination measures should take place prior to patient transport to a medical center. First responders and health care professionals should in turn take precautions not to intoxicate themselves through direct mouth-to-mouth resuscitative efforts (Riordan *et al.*, 2002). They must also wear personal protective equipment when transporting the victims to areas with adequate ventilation (Rotenberg, 2003a). Clothes are an obvious source for recontamination of the victim and must be removed. The skin should be subsequently flushed with copious volumes of water. The temperature of the water becomes a major consideration for children who may not tolerate extremes of cold or hot. Depending on the hospital size, antidote kits may or may not be available. Therefore, the time when supportive care is implemented becomes extremely important.

8. Antidotal Therapy

The US standard cyanide antidote kit uses a small inhaled dose of amyl nitrite followed by intravenous sodium nitrite and sodium thiosulfate (Rotenberg, 2003a; Anon, 1998). This antidote converts a portion of the hemoglobin's iron from ferrous iron to ferric iron, converting the hemoglobin into methemoglobin. Cyanide is more strongly drawn to methemoglobin than to the cytochrome oxidase of cells, effectively pulling the cyanide off the cells and onto the methemoglobin (Baskin and Brewer, 1997; Berlin, 1970). Once bound with the cyanide, the methemoglobin becomes cyanmethemoglobin (Anon, 1998). Therapy with nitrites is not innocuous, since methemoglobin cannot transport oxygen in the blood. The doses given to an adult can potentially cause a fatal methemoglobinemia in children or may cause profound hypotension. Treatment of children affected with cyanide intoxication must be individualized and is based upon their body weight and hemoglobin concentration. Once an ampule of amyl nitrite has been broken one at a time into a handkerchief, the contents should be held in front of the patient's mouth for 15 s, followed by 15 s of rest. This should be reapplied using this interrupted schedule until sodium nitrite can be administered. Continuous use of amyl nitrite may prevent adequate oxygenation. Taylor Pharmaceuticals, the manufacturer of the kit, recommends the dose for children of sodium nitrite to be 6 to 8 ml/m^2 (approximately 0.2 ml/kg body weight) but not to exceed an adult dose of 10 ml of a 3% solution (approximately 300 mg). While excessive sodium nitrite can cause methemoglobinemia, it should be noted that in the 70-year history of using the kit, the only reported fatality of such toxicity from using the kit involved a child without serious cyanide poisoning who was given two adult doses of sodium nitrite (Berlin, 1970; Hall and Rumack, 1986). In fact, the scientific literature recommends pediatric dosing based on monitoring hemoglobin levels. The next part of the cyanide

TABLE 61.7. Management of cyanide exposures (Anon, 1998; Berlin, 1970; Hall and Rumack, 1986)

Agent	Severity of symptoms	Antidotes/treatment			
		Multistage antidote kit (for unconscious patients)			
		Age	Amyl nitrite ampules	Sodium nitrite (for Hb = 12)	Sodium thiosulfate (for Hb = 12)
Cyanide	• Tachypnea • Restlessness • Anxiety • Flushing • Tachycardia • Dizziness • Apnea • Respiratory failure • Seizures • Coma	Child <30 kg	1. Crush 1 amp. in gauze close to the mouth and nose of breathing victim 2. Inhale for 15 s, rest for 15 s 3. Replace pearls every 30 s until sodium nitrite can be administered	1. 0.19–0.39 ml/kg not to exceed 10 ml of 3% solution slow IV over less than 5 min or slower if hypotension develops 2. For every 1 g/dl increase or decrease change in Hb, change dose by approximately 0.03 ml/kg accordingly 3. May repeat dose at 1/2 original dose in 30 min if needed	1. 0.95–1.95 ml/kg not to exceed 50 ml of 25% solution IV over 10–20 min 2. For every increase or decrease change in Hb of 1 g/dl, change sodium thiosulfate by 0.15 ml/kg accordingly 3. May repeat dose at 1/2 original dose in 30 min if needed
		Adult	See above	10 ml of 3% solution slow IV over no less than 5 min or slower if hypotension develops	50 ml of 25% solution IV over 10–20 min

Other treatment: evacuation, decontamination, 100% O_2, and correction of acidosis, hypovolemia, and seizures

antidote kit is sodium thiosulfate, which is administered intravenously (Rotenberg, 2003a; Baskin and Brewer, 1997; Anon, 1998; Hall and Rumack, 1986). The sodium thiosulfate and cyanmethemoglobin become thiocyanate, releasing hemoglobin; thiocyanate is excreted by the kidneys. Table 61.8 provides a dosing chart for the safe dosing of sodium nitrite and sodium thiosulfate with continuous monitoring of hemoglobin levels. Before treating pediatric patients with nitrites, it is imperative that prescribers inquire about conditions that may predispose a victim to anemia and, if there are concerns, doses should be decreased. Methemoglobin levels must be monitored sequentially in children and should not exceed 20% (Rotenberg, 2003a). Due to concerns about the excessive methemoglobinemia, along with the complicated administration procedures associated with the cyanide antidote kit, experts have suggested that alternative therapies may be preferable to use in children such as hydroxocobalamin (Geller *et al.*, 2006).

9. Alternative Strategies

Alternative methods of treating cyanide intoxication are used in other countries. For example, the antidote used primarily in France is hydroxocobalamin (a form of vitamin B_{12}), which combines with cyanide to form the harmless vitamin B_{12a} cyanocobalamin (Rotenberg, 2003a; Baskin and Brewer, 1997). In France, this medication is used for children at a dose of 70 mg/kg. A study of 41 French children with fire smoke inhalation showed a prehospital mortality rate of 4% for those given hydroxocobalamin and not found in cardiac arrest (Geller *et al.*, 2006). Authors of the study noted that for those children found in cardiac arrest by paramedics, administration of hydroxocobalmin

TABLE 61.8. Variation of sodium nitrite and sodium thiosulfate dose with hemoglobin concentration (Anon, 1998; Berlin, 1970; Hall and Rumack, 1986)

Hemoglobin (g/dl)	Initial IV dose sodium nitrite 3% (ml/kg) *Do not exceed 10 ml total dose*	Initial IV dose sodium thiosulfate 25% (ml/kg) *Do not exceed 50 ml total dose*
7	0.19	0.95
8	0.22	1.10
9	0.25	1.25
10	0.27	1.35
11	0.3	1.50
12	0.33	1.65
13	0.36	1.80
14	0.39	1.95

did not prevent any mortality. Another case series detailed eight pediatric patients exposed to cassava where four of the most severely affected children were given the cyanide antidote kit, while the four others were given 500 mg of hydroxocobalamin. All children improved regardless of which therapy they were given and were discharged from the hospital with no sequelae. This medication appears to have a good safety profile with adverse effects reported such as transient reddish-brown discoloration of the urine and mucous membranes. Some elevations in blood pressure and rash have also been reported (Geller *et al.*, 2006). The FDA approved hydroxocobalamin for use in the USA in December of 2006 to treat cyanide exposure victims in a product called Cyanokit®, manufactured by EMD Pharmaceuticals, Inc. The package insert for this medication provides adult dosing and a statement that the safety and effectiveness of the Cyanokit has not been established in the pediatric population. However, there is a reference to the 70 mg/kg dose which is used in Europe (Anon, 2006).

10. Summary

Cyanide is found in a wide variety of industrial processes and has been explored by Al Qaeda for use as a weapon of terror (Rotenberg, 2003a). Whether ingested or inhaled, cyanide is very lethal. Cyanide produces toxicity through impairment of mitochondrial enzymes, disrupting the electron transport chain, and preventing their utilization of oxygen. The mainstay of treatment of cyanide toxicity consists of use of a multistage antidote kit. The management of children with cyanide toxicity should include appropriate antidote dose adjustments and proper monitoring to prevent fatal methemoglobinemia. Another antidote, hydroxocobalamin, may gain favor over time as the treatment of choice for pediatric cyanide exposures, due to its preferable safety profile and its ease of administration (Geller *et al.*, 2006).

VI. DECONTAMINATION OF CHILDREN

Decontamination after a chemical terrorist attack needs to be well planned, efficient, and cognizant of the special needs of children. It is well recognized that the unique vulnerabilities of children may lead to a disproportionate number of pediatric victims after a chemical attack. Without proper planning and consideration as to how children will be decontaminated, the potential for preventable pediatric casualties is increased due to time loss and confusion. It is highly recommended for pediatricians to be involved in the development of each hospital's plans for decontamination. Over the last several years, many advances have been made in the management of the critically injured child. In fact, studies have shown that children managed in a pediatric intensive care unit (PICU) have better outcomes than children managed in an adult intensive care unit (Wheeler and Poss, 2003). Not all hospitals have the resources to have their own PICU, but they need to be able to provide the initial resuscitation and stabilization of pediatric victims of a terrorist attack. It is highly recommended that predetermined, written transfer agreements exist between emergency departments in community hospitals and centers that specialize in pediatric care. These agreements will allow the rapid transport of critically injured children to the sites that can ensure the best outcomes.

The first step in the decontamination process is the appropriate triage of patients (Burklow *et al.*, 2003). If this step is done quickly and accurately, patients will be appropriately managed and outcomes will improve. The key to triage is the ability to ration care when resources are limited. Victims are usually classified into tiered categories. Classic categories that have been used on the battlefield include minimal, delayed, immediate, and expectant. Patients in the minimal category have minor injuries that may not require medical care or can be managed with self-care. However, it should be noted that it is difficult for children to manage themselves, in addition to the fact that the category they are placed within can change more rapidly than that seen in adults. The delayed category describes patients who have injuries that will require medical intervention, but the injuries are not immediately life threatening. Logically, the immediate category describes patients who are critically injured and need medical intervention to save life or limb. Finally, the expectant category describes those patients who are so critically injured that they are not expected to survive. The expectant category poses a special challenge to civilian health care workers who are used to expending vast resources and personnel to maximize survival. In a mass casualty event, clinicians need to come to grips with the fact that the most ill may not be treated. Although the classic categories of triage are fairly well known, they are not consistently used among hospitals. Some categories are developed specific to chemical attacks. An example of this are triage categories that separate patients as "exposed" or "not exposed". At the University of Maryland Medical Center, the biochemical response triage categories differentiate between exposed and not exposed individuals. Furthermore, recognizing that not all exposed individuals will necessarily be symptomatic but may still need to be isolated, the categories differentiate between those who are asymptomatic, exposed and symptomatic, exposed and asymptomatic, and those with unrelated emergent conditions. Regardless of what categories get utilized, triage must focus on the fact that the best outcome is achieved for the greatest number of victims. To achieve this outcome, appropriate identification of the causative agent is critical. This can be a challenge because often full identification is delayed. To protect those involved in triage, full personal protective equipment is highly recommended. Work in full personal equipment can be cumbersome and uncomfortable, but when triage is done correctly, unnecessary decontamination can be avoided.

After triage, the decontamination process should begin (Wheeler and Poss, 2003). All workers who are involved in

this process must be appropriately protected with butyl rubber aprons and gloves, double layers of latex gloves, waterproof aprons, and chemical resistant jumpsuits. Personal protective equipment should also include an appropriately selected air-purifying or atmosphere-supplying respirator, depending upon how well the threat environment has been categorized. It is important to note that this equipment often needs to be changed to prevent health care worker exposure.

The set up and use of the decontamination area must be carefully thought out. Often, the area is split into different zones (Rotenberg *et al.*, 2003). At a minimum, there must be a dirty contaminated zone and a clean decontaminated zone. It is critical to emphasize that traffic must go one-way between zones. This will eliminate the possibility of a cleaned patient becoming cross-contaminated or an exposed patient entering a health care facility before being decontaminated. Security personnel must be utilized to make sure patients do not consciously or unconsciously violate the rules. A secondary triage will be needed as patients enter the clean zone to allow patients to receive antidotes or be referred for further care. Keep in mind that for severely ill patients, antidote administration may precede decontamination.

The selection of the appropriate decontamination agent is important. The gold standard for decontamination is plain water (Rotenberg *et al.*, 2003). Other agents that have been used for decontamination include carbonaceous adsorbent powder, dilute (0.5%) hypochlorite solution, water with soap, and dry decontaminants such as flour or talcum powder. For children, the use or water or water with soap is preferred. In addition to agents used to decontaminate, other cornerstones to management include exposure to fresh air when patients have been exposed to chemicals in the gaseous form, a change of clothing, and showers.

Conducting decontamination in children can be especially difficult. At every step of the process, there are special considerations that need to be addressed (Rotenberg *et al.*, 2003). Starting at triage, clinicians need to understand how chemical toxicities manifest in children; also an understanding of what normal vital signs should be for a child will be critical. Pediatric-specific triage tools often consider different vital signs such as heart rate and respiratory rate parameters and the differing ability of patients to communicate. It is important for the triage to include the examination of the child's mouth and eyes because of frequent hand-to-mouth and hand-to-eye activity. If antidote administration is needed, pediatric references should be readily available, and an understanding of pediatric doses will be needed. When there is a lack of experience with managing children, the otherwise efficient decontamination process can get bogged down. Some hospitals have decided to set up pediatric-specific areas to address the specific needs of children.

Clinicians may need to handle uncooperative or nonverbal children. This becomes especially challenging when an intravenous line needs to be started. Placing a line in a child while in full protective equipment is no small feat. Also, keep in mind that the unfamiliar presence of a clinician in full personal protective equipment can cause fear and distress in a child. Children undergoing decontamination will benefit from a guardian to guide them through and reassure them. For those children who present alone, a guardian will need to be appointed and a system for parental identification will be needed. Hospitals will need to plan for this extra resource. In fact, one Israeli hospital has employed social workers in their disaster preparation to help manage patient/family needs and psychological distress (Rosenbaum, 1993). It is recommended not to separate parents and children during a time of crisis. Plans should be made for the decontamination and treatment of parent–child pairs (Rotenberg *et al.*, 2003).

A range of specially sized supplies is needed to appropriately manage children, which range from pediatric-sized emergency equipment to basic needs such as formula for feeding and diapers for hygiene. Since decontamination often includes disrobing, pediatric-sized clothing would be needed. For children who may need to be observed for hours, toys will be needed.

Also, the agents used to decontaminate children should be carefully selected. Bleach or hypochlorite solutions are not recommended for use with children due to the possibility of skin irritation or damage (Rotenberg *et al.*, 2003). Water is the gold standard for decontamination. When employing water decontamination, the temperature of the water must be addressed. Children, especially newborns and infants, are prone to hypothermia and hemodynamic instability from cold water. Water at a comfortable temperature is recommended along with a good supply of blankets which can be used to quickly warm up pediatric patients after water decontamination. In some situations, indoor sprinkler systems have been used when outdoor conditions were inhospitable.

VII. PREPARATION FOR A CHEMICAL EVENT

Understanding chemical agents used for terrorism and knowing how to manage toxicity is just the first step in preparing for a chemical event. Appropriate training on how to manage pediatric patients in these scenarios is critical. Pediatricians are uniquely trained to participate in the management of pediatric casualties and to advocate for children so that their needs are addressed in emergency planning (Bradley *et al.*, 2003). Many hospitals have held emergency exercises to see how prepared they are for these situations. Beyond this, the assessments should identify deficits and should be used to forge partnerships and relationships and share assets in the community to manage every possible scenario (Blaschke *et al.*, 2003). Health care facilities responsible for treating pediatric victims in

TABLE 61.9. Example pediatric specific hospital emergency drug cache

Drug	Strength	Dosage form	Pediatric dosing	Therapy or prophylaxis	Disease
Albuterol MDI	17 gm	INH	2–4 puffs q4h	Respiratory distress from chemical agents	Chemical exposure
Amoxicillin oral suspension	400 mg/5 ml 100 ml	Oral suspension	15 mg/kg q8h – up to 40 kg, >40 kg 500 mg q8h	Chemoprophylaxis	Anthrax
Atropine	1 mg/ml	Injection	See dosing table	Chemotherapy	Nerve agent exposure
Ciprofloxacin oral suspension	250 mg/5 ml 100 ml	Oral suspension	20–30 mg/kg/day divided q12h for 60 days	Chemoprophylaxis	Anthrax, plaque
Clindamycin	600 mg/NS 50 ml	IVPB	30 mg/kg/day q8h (max 4.8 g/day)	Chemotherapy	Anthrax
Cyanide antidote package	1 kit	Kit	See dosing table	Chemotherapy	Cyanide poisoning
Diazepam IV	5 mg/ml ×2 ml	Injection	See dosing table	Seizures post chemical exposure	SZ post-chemical exposure
Doxycycline oral suspension	25 mg/5 ml 60 ml	Oral suspension	2.5 mg/kg q12h – up to 40 kg, >40 kg 100 mg q12h for 60 days	Chemoprophylaxis	Anthrax, cholera, brucellosis, plague
Oseltamivir suspension	12 mg/ml 25 ml	Suspension	For children ≥1–12 yrs: ≤15 kg: 2 mg/kg/dose (max 30 mg) BID × 5 days, >15–23 kg: 45 mg/dose BID × 5 days, >23–40 kg: 60 mg/dose BID × 5 days, >40 kg 75 mg/dose BID × 5 days	Chemotherapy	Avian influenza
Potassium iodide	65 mg	Tablet	4–18 yrs: 65 mg, 1 mo–3 yrs: 32.5 mg, <1 mo: 16.25 mg	Chemotherapy	Radiation emergency
Pralidoxime	1 gm/20 ml SDV	Powder for injection	See dosing table	Chemotherapy	Nerve agent exposure
Ribavirin solution	40 mg/ml 100 ml	Solution	LD 30 mg/kg followed by 15 mg/kg/day BID × 10 days	Chemotherapy	Viral hemorrhagic fever

a chemical–biological event could be easily strained and overwhelmed. Often large-scale chemical–biological incidents necessitate the use of alternative areas to triage patients such as auditoriums and arenas. These alternative triage areas need to know how to manage pediatric victims (CEH/CID, 2000). Planning for an attack begins with the development of local health resources. Unfortunately, with chemical releases, clinical effects can occur extremely quickly, limiting time to borrow resources from nearby communities. First responders must be educated to recognize pediatric signs and symptoms from each chemical agent, how to wear protective gear in the face of persistent agents, handle pediatric patients, and be able to manage field decontamination. It is critical that adequate supplies of protective gear are available. When planning for decontamination procedures, pediatric vulnerabilities and challenges need to be considered such as the temperature of the water and the ability of children to follow directions.

Since children spend the majority of the day at school, community preparation for a threat must include the local educational system. Development of a rapid evacuation plan and the establishment of in-school shelters are critical. Schools can play a valuable role for the management of pediatric casualties.

Another key element to appropriate preparedness is the development of a pharmaceutical cache of antidotes, antibiotics, and vaccines. This cache will play a key role in the initial management of a chemical attack. Even though the SNS is now in place throughout the USA, it may be several hours before it reaches a hospital and the supply is divided among several sites. The SNS has made efforts to include pediatric-ready medications such as suspensions and solutions. Efforts must be made for local pharmaceutical caches to address pediatric needs. An example of a pediatric pharmaceutical cache is displayed in Table 61.9.

VIII. CONCLUDING REMARKS AND FUTURE DIRECTION

Much progress has been made in understanding how pediatric patients need to be managed when they are affected by chemical agents. Several pediatric organizations, such as the AAP, have given guidance on how best to handle these situations. It is a special challenge to gather information regarding pediatric chemical casualties because our experience is so limited. Further research and resources are needed to fully understand all the physical and psychological impacts a terror attack has on children. The intention of this work is to provide a framework from which local and national efforts can grow. In the event of a chemical attack, prior preparation and planning will make the difference to whether lives are saved or further lives are lost. Efforts to improve upon current recommendations for managing pediatric chemical casualties must continue in order to better protect this vulnerable population.

References

Abraham, R.B., Weinbroum, A.A., Rudick, V., Paret, G. (2001). Perioperative care of children with nerve agent intoxication. *Paediatr. Anaesth.* **11**: 643–9.

Abraham, R.B., Rudick, V., Weinbroum, A.A. (2002). Practical guidelines for acute care of victims of bioterrorism: conventional injuries and concomitant nerve agent intoxication. *Anesthesiology* **97**: 989–1004.

Amitai, Y., Almog, S., Singer, R., Hammer, R., Bentur, Y., Danon, Y.L. (1999). Atropine poisoning in children during the Persian Gulf crisis: a national survey in Israel. *JAMA* **268**: 630–2.

Anon (Anonymous) (1998). Cyanide antidote package insert. Taylor Pharmaceuticals™. Latest update, July 1998.

Anon (Anonymous) (2002). Pralidoxime (2 PAM) package insert. Meridian Medical Technologies™, Inc. Latest update, May 2002.

Anon (Anonymous) (2006). Cyanokit® package insert. EMD Pharmaceuticals, Inc.™. Latest update, December 2006.

ARC (Applied Research and Consulting, LLC) (2002). Effects of the World Trade Center attack on NYC public school students: initial report to the New York City Board of Education. Columbia University Mailman School of Public Health, New York State Psychiatric Institute, May 6, 2002.

Augustinsson, K.B., Brody, S. (1962). Plasma arylesterase activity in adults and newborn infants. *Clin. Chim. Acta* **7**: 560–5.

Azizi, M.D., Amid, M.H. (1990). Clinical presentation of chemical warfare injuries in children and teenagers. *Med. J. Islamic Rep. Iran* **4**: 103–8.

Baskin, S.I., Brewer, T.G. (1997). Cyanide poisoning. In *Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare. Part I, Warfare, Weaponry, and the Casualty* (R. Zajtchuk, ed.). Borden Institute, Walter Reed Army Medical Center, Washington, DC.

Behrendt, H., Green, M. (1958). Skin pH pattern in the newborn infant. *Am. J. Dis. Child* **95**: 35–41.

Bennett, W.D., Zeman, K.L. (1998). Deposition of fine particles in children spontaneously breathing at rest. *Inhal. Toxicol.* **10**: 831–42.

Berlin, C.M. (1970). The treatment of cyanide poisoning in children. *Pediatrics* **46**: 793–6.

Besunder, J.B., Reed, M.D., Blumer, J.L. (1988). Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic–pharmacodynamic interface. (Part I). *Clin. Pharmacokinet.* **14**: 261–86.

Blaschke, G.S., Lynch, J. (2003). Terrorism: its impact on primary pediatrics, part I. *Pediatr. Ann.* **32**: 80–4.

Blaschke, G.S., Palfrey, J.S., Lynch, J. (2003). Advocating for children during uncertain times. *Pediatr. Ann.* **32**: 271–4.

Bradley, B.J., Gresham, L.S., Sidelinger, D.E., Hartstein, B.H. (2003). Pediatric health professionals and public health response. *Pediatr. Ann.* **32**: 87–94.

Bronstein, A.C., Spyker, D.A., Cantilena, L.R., Green, G., Rumack, B.H., Heard, S.E. (2007). 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). *Clin. Toxicol.* **45**: 815–917.

Buchholz, U., Mermin, J., Rios, R., Casagrande, T.L., Galey, F., Lee, M., Quattrone, A., Farrar, J., Nagelkerke, N., Werner, S.B. (2002). An outbreak of food-borne illness associated with methomyl-contaminated salt. *JAMA* **288**: 604–10.

Burklow, T.R., Yu, C.E., Madsen, J.M. (2003). Industrial chemicals: terrorist weapons of opportunity. *Pediatr. Ann.* **32**: 230–4.

Buscher, H., Conway, N. (1944). *Green and Yellow Cross.* Kettering Laboratory of Applied Physiology, University of Cincinnati, Cincinnati, Ohio.

Caravati, E.M., Litovitz, T.L. (1988). Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *JAMA* **260**: 3470–3.

Clewell, H.J., Teeguarden, J., McDonald, T., Sarangapani, R., Lawrence, G., Covington, T., Gentry, R., Shipp, A. (2002). Review and evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Crit. Rev. Toxicol.* **32**: 329–89.

CEH/CID (Committee on Environmental Health and Committee on Infectious Diseases) (2000). Chemical–biological terrorism and its impact on children: a subject review. *Pediatrics* **105**: 662–70.

CEH/CID (Committee on Environmental Health and Committee on Infectious Diseases) (2006). Chemical–biological terrorism and its impact on children. *Pediatrics* **118**: 1267–78.

CSMC (Cedars-Sinai Medical Center) (2003). Children more vulnerable than adults in the event of a chemical spill or chemical weapons attack. Cedars-Sinai Medical Center News. July 14, 2003.

DCI (Director of Central Intelligence) (2002). Unclassified report to Congress on the acquisition of technology relating to weapons of mass destruction and advanced conventional munitions, 1 January through 30 June 2003. 2001 CIA Congressional Report. DCI Weapons Intelligence, Nonproliferation, and Arms Control Center (WINPAC), Washington, DC.

de Tollenaer, S.M., Buysse, C., Van den Anker, J.N., Touw, D.J., de Hoog, M. (2006). Life threatening central nervous system manifestations and hypothermia due to maneb intoxication in a child: a case report. *Ther. Drug Monit.* **28**: 813–15.

Dompeling, E., Jöbsis, Q., Vandevijver, N.M., Wesseling, G., Hendriks, H. (2004). Chronic bronchiolitis in a 5-yr-old child after exposure to sulfur mustard gas. *Eur. Respir. J.* **23**: 343–6.

Dunn, M.A., Sidell, F.R. (1989). Progress in medical defense against nerve agents. *JAMA* **262**: 649–52.

Ecobichon, D.J., Stephens, D.S. (1973). Perinatal development of human blood esterases. *Clin. Pharmacol. Ther.* **14**: 41–7.

Fairley, J.A., Rasmussen, J.E. (1983). Comparison of stratum corneum thickness in children and adults. *J. Am. Acad. Dermatol.* **8**: 652–4.

Fluhr, J.W., Pfisterer, S., Gloor, M. (2000). Direct comparison of skin physiology in children and adults with bioengineering methods. *Pediatr. Dermatol.* **17**: 436–9.

Fluhr, J.W., Behne, M.J., Brown, B.E., Moskowitz, D.G., Selden, C., Mao-Wiang, M., Mauro, T.M., Elias, P.M., Feingold, K.R. (2004). Stratum corneum acidification in neonatal skin: secretory phospholipase A2 and the sodium/hydrogen antiporter-1 acidify neonatal rat stratum corneum. *J. Invest. Dermatol.* **122**: 320–9.

Foroutan, S.A. (1996a). Medical notes concerning chemical warfare, Part I. [original in Farsi]. *Kowsar Med. J.* **1(1)**: 1–8.

Foroutan, S.A. (1996b). Medical notes concerning chemical warfare, Part II. [original in Farsi]. *Kowsar Med. J.* **1(2)**: 1–23.

Foroutan, S.A. (1998a). Medical notes concerning chemical warfare, Part VI. [original in Farsi]. *Kowsar Med. J.* **2(4)**; 1–18.

Foroutan, S.A. (1998b). Medical notes concerning chemical warfare, Part VII. [original in Farsi]. *Kowsar Med. J.* **3(1)**: 1–10.

Foroutan, S.A. (1998c). Medical notes concerning chemical warfare, Part IX. [original in Farsi]. *Kowsar Med. J.* **3(3)**: 1–16.

Geffner, M.E., Powars, D.R., Choctaw, W.T. (1981). Acquired methemoglobinemia. *West. J. Med.* **134**: 7–10.

Geller, R.J., Barthold, C., Saiers, J.A., Hall, A.H. (2006). Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics* **118**: 2146–58.

Ginsberg, G., Hattis, D., Sonawane, B. (2004). Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. *Toxicol. Appl. Pharmacol.* **198**: 164–83.

Goldfrank, L.R., Flomenbaum, N.E., Lewin, N.A. (1998). Cyanide and hydrogen sulfide. In *Goldfrank's Toxicologic Emergencies*, 6th edition. Appleton & Lange, Stamford, CT.

Graham, J.S., Chilcott, R.P., Rice, P., Milner, S.M., Hurst, C.G., Maliner, B.I. (2005). Wound healing of cutaneous sulfur mustard injuries: strategies for the development of improved therapies. *J. Burns Wounds* **4**: e(electronic article)1.

Güloğlu, C., Kara, I.H., Erten, P.G. (2002). Acute accidental exposure to chlorine gas in the southeast of Turkey: a study of 106 cases. *Environ. Res.* **88**: 89–93.

Guyton, A.C., Hall, J.E. (2005). *Textbook of Medical Physiology*, 11th edition. W.B. Saunders Company, Philadelphia, PA.

Hall, A.H., Rumack, B.H. (1986). Clinical toxicology of cyanide. *Ann. Emerg. Med.* **15**: 1067–74.

Harpin, V.A., Rutter, N. (1983). Barrier properties of the newborn infant's skin. *J. Pediatr.* **102**: 419–25.

Hay, A., Roberts, G. (1990). The use of poison gas against the Iraqi Kurds: analysis of bomb fragments, soil, and wool samples. *JAMA* **263**: 1065–6.

Henretig, F.M., Cieslak, T.J., Eitzen, E.M., Jr. (2002a). Medical progress: biological and chemical terrorism. *J. Pediatr.* **141**: 311–26.

Henretig, F.M., Cieslak, T.J., Eitzen, E.M. (2002b). Medical progress: biological and chemical terrorism erratum. *J. Pediatr.* **141**: 743–6.

Hilmas, C., Adler, M., Baskin, S.I. (2006). Pulmonary toxicity of cholinesterase inhibitors. In *Toxicology of Organophosphate and Carbamate Compounds* (R.C. Gupta, ed.), pp. 389–98. Elsevier Academic Press, San Diego, CA.

Holland, N., Furlong, C., Bastaki, M., Richter, R., Bradman, A., Huen, K., Beckman, K., Eskenazi, B. (2006). Paraoxonase polymorphisms, haplotypes, and enzyme activity in Latino mothers and newborns. *Environ. Health Perspect.* **114**: 985–91.

Kearns, G.L., Reed, M.D. (1989). Clinical pharmacokinetics in infants and children. A reappraisal. *Clin. Pharmacokinet.* **17** (Suppl. 1): 29–67.

Lehmann, H., Cook, J., Ryan, E. (1957). Pseudocholinesterase in early infancy. *Proc. R. Soc. Med.* **50**: 147–50.

Levy-Khademi, F., Tenenbaum, A.N., Wexler, I.D., Amitai, Y. (2007). Unintentional organophosphate intoxication in children. *Pediatr. Emerg. Care* **23**: 716–18.

Lifshitz, M., Rotenberg, M., Sofer, S., Tamiri, T., Almog, S. (1994). Carbamate poisoning and oxime treatment in children: a clinical and laboratory study. *Pediatrics* **93**: 652–5.

Lifshitz, M., Shahak, E., Sofer, S. (1999). Carbamate and organophosphate poisonings in young children. *Pediatr. Emerg. Care* **15**: 102–3.

Logan, T.P., Graham, J.S., Martin, J.L., Zallnick, J.E., Jakubowski, E.M., Braue, E.H. (2000). Detection and measurement of sulfur mustard (HD) offgassing from the weanling pig following exposure to saturated sulfur mustard vapor. *J. Appl. Toxicol.* **20**: S199–204.

Lynch, E.L., Thomas, T.L. (2004). Pediatric considerations in chemical exposures: are we prepared? *Pediatr. Emerg. Care* **20**: 198–205.

Mancini, A.J. (2004). Skin. *Pediatrics* **113** (Suppl. 4): 1114–19.

Markenson, D., Redlener, I. (2004). Pediatric terrorism preparedness national guidelines and recommendations: findings of an evidenced-based consensus process. *Biosecur. Bioterror.* **2**: 301–9.

Marshall, J.H., Bromberg, B.E., Adrizzo, J.R., Heurich, A.E., Samet, C.M. (1972). Fatal tetanus complicating a small partial-thickness burn. *J. Trauma* **12**: 91–3.

Martonen, T.B., Musante, C.J., Sega, R.A., Schroeter, J.D., Hwang, D., Dolovich, M.A., Burton, R., Spencer, R.M., Fleming, J.S. (2000). Lung models: strengths and weaknesses. *Respir. Care.* **45**: 712–36.

Meadows, M. (2004). The FDA and the fight against terrorism. *FDA Consum.* **38**: 20–7.

Momeni, A., Aminjavaheri, M. (1994). Skin manifestations of mustard gas in a group of 14 children and teenagers: a clinical study. *Int. J. Dermatol.* **33**: 184–7.

Montello, M.J., Tarosky, M., Pincock, L., Montello, N., Hess, W.A., Velazquez, L., Patel, A., Krzyworzeka, J., Hay, E. (2006). Dosing cards for treatment of children exposed to weapons of mass destruction. *Am. J. Health Syst. Pharm.* **63**: 944–9.

Moradi, A., Sodeifi, M., Abdollahi, B., Pakdaman, A., Vessal, K. (1986). Clinical presentation of chemical warfare injuries. *Iran J. Med. Sci.* **13**: 1–5.

Morselli, P.L. (1976). Clinical pharmacokinetics in neonates. *Clin. Pharmacokinet.* **1**: 81–98.

Morselli, P.L. (1989). Clinical pharmacology of the perinatal period and early infancy. *Clin. Pharmacokinet.* **17** (Suppl. 1): 13–28.

Motakallem, M.H. (1988). Evaluation of 17 patients severely injured with sulfur mustard. *Med. J. Islamic Rep. Iran* **2**: 99–104.

Nopper, A.J., Horii, K.A., Sookdeo-Drost, S., Wang, T.H., Mancini, A.J., Lane, A.T. (1996). Topical ointment therapy benefits premature infants. *J. Pediatr.* **128**: 660–9.

NRC (National Research Council) (1993). *Pesticides in the Diets of Infants and Children.* National Academy Press, Washington, DC.

Ohlgisser, M., Adler, M., Ben-Dov, D., Taitelman, U., Birkhan, H.J., Bursztein, S. (1978). Methaemoglobinaemia induced by mafenide acetate in children. *Br. J. Anaesth.* **50**: 299–301.

OPCW (Organization for the Prohibition of Chemical Weapons) (2005). Annex on Chemicals. In *Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction*, pp. 51–4. Technical Secretariat, OPCW.

PEAP (Pediatric Expert Advisory Panel) (2004). Atropine use in children after nerve gas exposure. Columbia University Mailman School of Public Health **1**: 1–8.

Peden, N.R., Taha, A., McSorley, P.D., Bryden, G.T., Murdoch, I.B., Anderson, J.M. (1986). Industrial exposure to hydrogen cyanide: implications for treatment. *Br. Med. J.* **293**: 538.

Pherwani, A.V., Khanna, S.A., Patel, R.B. (1989). Effect of chlorine gas leak on the pulmonary functions of school children. *Indian J. Pediatr.* **56**: 125–8.

Prajapati, N.C., Puri, R.K., Sarangi, M.P., Yadav, S., Khalil, A. (1992). Potassium cyanide poisoning. *Indian Pediatr.* **29**: 903–5.

Riordan, M., Rylance, G., Berry, K. (2002). Poisoning in children: 5 rare and dangerous poisons. *Arch. Dis. Child.* **87**: 407–10.

Rolfsjord, L.B., Fjaerli, H.O., Meidel, N., Stromme, J.H., Kowalczyk, M., Jacobsen, D. (1998). Severe organophosphate (demeton-s-methyl) poisoning in a two-year-old child. *Vet. Hum. Toxicol.* **40**: 222–4.

Rosenbaum, C. (1993). Chemical warfare: disaster preparation in an Israeli hospital. *Soc. Work Health Care* **18**: 137–45.

Rotenberg, J.S. (2003a). Cyanide as a weapon of terror. *Pediatr. Ann.* **32**: 236–40.

Rotenberg, J.S. (2003b). Diagnosis and management of nerve agent exposure. *Pediatr. Ann.* **32**: 242–50.

Rotenberg, J.S., Newmark, J. (2003). Nerve agent attacks on children: diagnosis and management. *Pediatrics* **112**: 648–58.

Rotenberg, J.S., Burklow, T.R., Selanikio, J.S. (2003). Weapons of mass destruction: the decontamination of children. *Pediatr. Ann.* **32**: 261–7.

Ruhl, C.M., Park, D.J., Danisa, O., Morgan, R.F., Papirmeister, B., Sidell, F.R., Edlich, R.F., Anthony, L.S., Himel, H.N. (1994). A serious skin sulfur mustard burn from an artillery shell. *J. Emerg. Med.* **12**: 159–66.

Rutter, N., Hull, D. (1979). Water loss from the skin of term and preterm babies. *Arch. Dis. Child.* **54**: 858–68.

Saunders, N.R., Knott, G.W., Dziegielewska, K.M. (2000). Barriers in the immature brain. *Cell. Mol. Neurobiol.* **20**: 29–40.

Schobitz, E.P., Schmidt, J.M., Poirier, M.P. (2008). Biological and chemical terrorism in children: an assessment of residents' knowledge. *Clin. Pediatr.* **47**: 267–70.

Schonfeld, D.J. (2003). Supporting children after terrorist events: potential roles for pediatricians. *Pediatr. Ann.* **32**: 182–7.

Seidenari, S., Giusti, G., Bertoni, L., Magnoni, C., Pellacani, G. (2000). Thickness and echogenicity of the skin in children as assessed by 20-MHz ultrasound. *Dermatology* **201**: 218–22.

Sidell, F.R., Urbanetti, J.S., Smith, W.J., Hurst, C.G. (1997). Vesicants. In *Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare. Part I, Warfare, Weaponry, and the Casualty* (R. Zajtchuk, ed.). Borden Institute, Walter Reed Army Medical Center, Washington, DC.

Simónen, P., O'Brien, M., Hamilton, C., Ashcroft, J., Denham, J. (1997). Normal variation in cutaneous blood content and red blood cell velocity in humans. *Physiol. Measure.* **18**: 155–70.

Sofer, S., Tal, A., Shahak, E. (1989). Carbamate and organophosphate poisoning in early childhood. *Pediatr. Emerg. Care* **5**: 222–5.

Stead, A.L. (1955). The response of the newborn infant to muscle relaxant. *Br. J. Anaesth.* **27**: 124–30.

Thomas, A. (1985). Effects of chemical warfare: a selective review and bibliography of British state papers. In *SIPRI Chemical & Biological Warfare Studies No. 1*, pp. 1, 20, 22. Taylor & Francis, Philadelphia, PA.

Traub, S.J., Hoffman, R.S., Nelson, L.S. (2002). Case report and literature review of chlorine gas toxicity. *Vet. Hum. Toxicol.* **44**: 235–9.

USAMRICD (US Army Medical Research Institute of Chemical Defense) (2000a). *Medical Management of Chemical Casualties Handbook*, 3rd edition Chemical Casualty Care Division, Aberdeen Proving Ground, MD.

USAMRICD (US Army Medical Research Institute of Chemical Defense) (2000b). *Field Management of Chemical Casualties Handbook*, 2nd edition. Chemical Casualty Care Division, Aberdeen Proving Ground, MD.

Vesicants (blister agents) (1996). *NATO Handbook on the Medical Aspects of NBC Defensive Operations, III: Chemical [AMedP-6(B) part III]*. Department of the Army, Washington, DC.

Weizman, Z., Sofer, S. (1992). Acute pancreatitis in children with anticholinesterase insecticide intoxication. *Pediatrics* **90**: 204–6.

West, J.B. (1995). Mechanics of breathing. In *Respiratory Physiology – The Essentials*, 5th edition (P.A. Coryell, ed.), pp. 103–5. Williams & Wilkins, Baltimore, MD.

Wheeler, D.S., Poss, W.B. (2003). Mass casualty management in a changing world. *Pediatr. Ann.* **32**: 98–105.

Yu, C.E., Burklow, T.R., Madsen, J.M. (2003). Vesicant agents and children. *Pediatr. Ann.* **32**: 254–7.

Zwiener, R.J., Ginsburg, C.M. (1988). Organophosphate and carbamate poisoning in infants and children. *Pediatrics* **81**: 121–6.